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Frontotemporal Dementias

Emerging Milestones of the 21st Century

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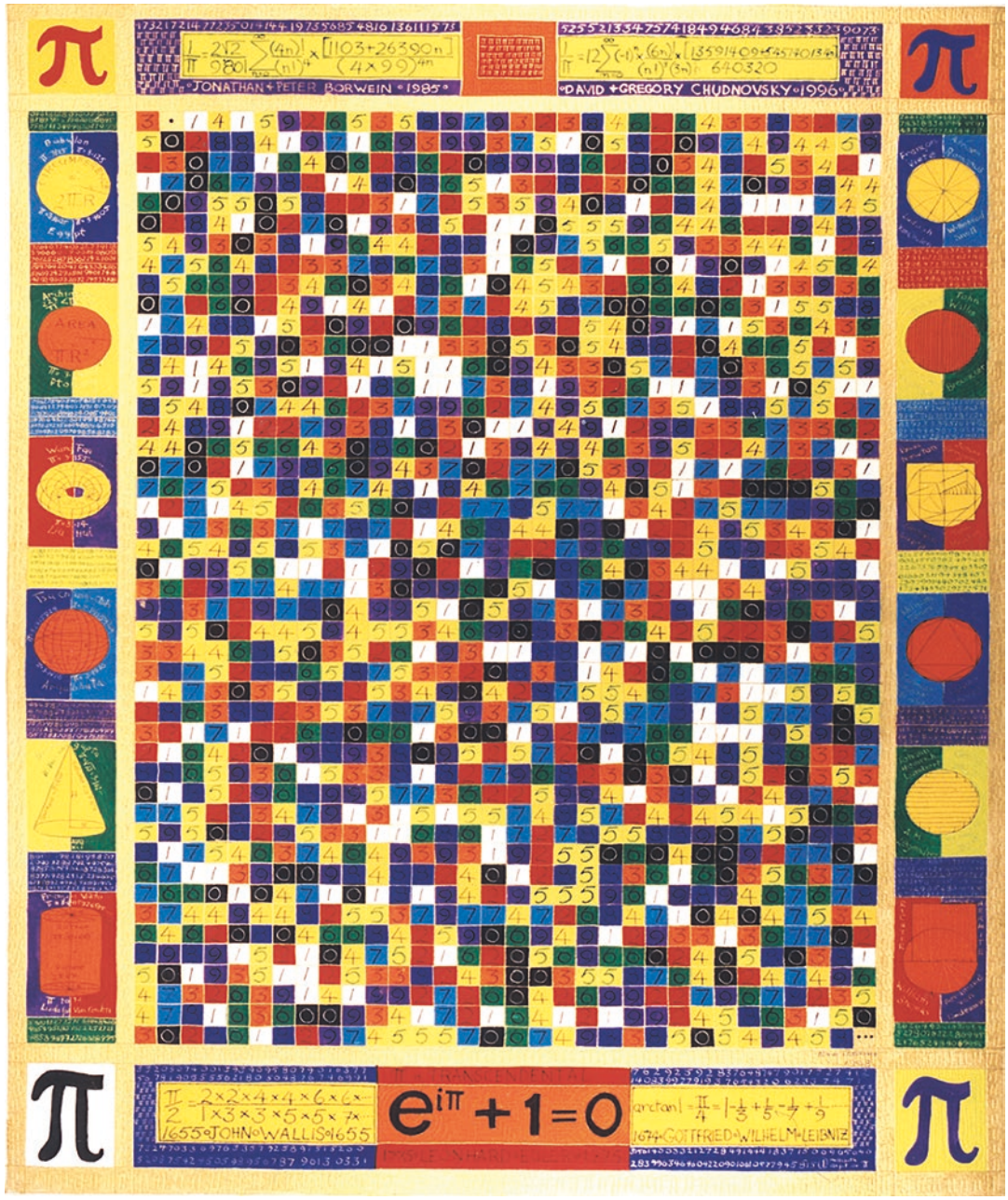

The image intended to represent visually the mathematical formula for Pi (π). The artwork was created by a patient with non-fluent Primary Progressive Aphasia (PPA)

Preface

The desire of giving a voice to the International Society for Frontotemporal Dementias provided the inspiration for bringing together modern pioneers and their trainees to share their awareness and vision about the diseases of the nervous system that destroy language and most human qualities. As the heritage of the founders of Frontotemporal Dementia research is legendary, nothing matters more than what we can promise and do next.

We have made the effort of identifying what we call "emerging milestones of the twenty-first century," building a bridge between the work of the founders and that of today's pioneers. Each chapter of the volume not only illustrates the present state of the art, but also reveals the challenges ahead. The original clinical and neuropathologic observations made in individuals affected by frontotemporal dementia are now investigated with the most advanced methods and continuously evolving instrumentation of microscopy and in vivo imaging that allow us to interrogate the biology of frontotemporal dementia at the molecular and soon at the atomic level. Discoveries made during the last two decades of the twentieth century have provided the foundations for new molecular investigations in the twenty-first century; in fact, protein chemistry and genetics have contributed to the exploration of unmapped territories, revealing how the words "frontotemporal dementia" includes a growing multiplicity of disorders.

Thus, the emerging milestones are meant to remind us that many miles are ahead for the International Society for Frontotemporal Dementias, before we reach the end of a journey which is challenging for science and perilous for the patients and the families that we, the members of the International Society for Frontotemporal Dementias, wish to help.

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Behavioural Variant Frontotemporal Dementia: Recent Advances in the Diagnosis and Understanding of the Disorder

Rebekah M. Ahmed, John R. Hodges, and Olivier Piguet

Introduction

Over the past 30 years, the understanding of the clinical phenomenology, neuroimaging, genetics and pathology of frontotemporal dementia (FTD) has undergone a metamorphosis. This has, in turn, opened the door to potential treatment trials, which would have been thought to be out of reach not that long ago. Since the original descriptions of FTD, originally known as Pick's disease, our ability to accurately diagnose and differentiate patients presenting with predominantly behavioural changes (so-called behavioural variant FTD) and with forms of primary progressive aphasias has improved considerably. Recently, the concept of frontotemporal lobar degeneration spectrum disorders has evolved to encompass the overlap between FTD and amyotrophic lateral sclerosis (ALS), as well as conditions such as progressive supranuclear palsy and corticobasal degeneration.

FTD primarily refers to a group of neurodegenerative brain disorders characterised by atrophy of the frontal and anterior temporal lobes. Prevalence studies suggest that FTD is the second most common cause of younger onset dementia [1, 2]. Three main clinical syndromes of FTD are generally recognised, based on their clinical presentations: a behavioural variant FTD (bvFTD) in which deterioration in social function and personality is most prominent and two language presentations, classified under primary progressive aphasia (PPA), in which an insidious decline in language skills is the primary feature. These PPAs are divided based on the pattern of language breakdown into semantic dementia (SD, also labelled semantic variant PPA) and progressive nonfluent aphasia (PNFA, also labelled nonfluent variant PPA) [3, 4]. Each of these syndromes has distinct clinical symptoms, imaging and pathological characteristics, although considerable heterogeneity and overlap exist in clinical practice, particularly as the disease progresses.

This chapter specifically focuses on bvFTD and on the recent advances in our understanding of the clinical features of this syndrome, its diag-

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nosis, including its overlap with ALS. Other chapters of this special issue will cover the genetic, pathological and imaging advances.

A major advance in the field of bvFTD was the publication, in 2011, of international consensus diagnostic criteria with increasing levels of diagnostic certainty (Table 1). At the lowest level of diagnostic certainty is possible bvFTD: a pure clinical diagnosis requiring the presence of three of six behavioural changes, namely disinhibition, apathy, loss of empathy, perseverative/compulsive behaviours, hyperorality and a dysexecutive neuropsychological profile. A diagnosis of probable bvFTD is based on the clinical syndrome, plus demonstrable functional decline and structural or functional changes in the frontotemporal regions on neuroimaging. A diagnosis of definite bvFTD is limited to those patients with the clinical syndrome and evidence of a pathogenic mutation or FTLD histopathology [5]. It has been shown that the probable level is robust and consistent when cases are followed over a number of years while only a half of those with possible bvFTD progress to clear-cut FTD over a 3-year follow-up period [6], and a proportion of such cases have the phenocopy syndrome discussed below.

Table 1 Key diagnostic symptoms of bvFTD, forming part of diagnostic criteria [5]

A. Early *behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
A.1. Socially inappropriate behaviour
A.2. Loss of manners or decorum
A.3. Impulsive, rash or careless actions
B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
B.1. Apathy
B.2. Inertia
C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
C.1. Diminished response to other people's needs and feelings
C.2. Diminished social interest, interrelatedness or personal warmth
D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
D.1. Simple repetitive movements
D.2. Complex, compulsive or ritualistic behaviours
D.3. Stereotypy of speech
E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
E.1. Altered food preferences
E.2. Binge eating, increased consumption of alcohol or cigarettes
E.3. Oral exploration or consumption of inedible objects
F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
F.1. Deficits in executive tasks
F.2. Relative sparing of episodic memory
F.3. Relative sparing of visuospatial skills

* Refers to symptom presentation within first 3 years

While in the early 2000s research understandably focused on cognition, it has become apparent that tests of executive dysfunction have limited specificity in detecting bvFTD. More recent studies have examined other aspects which are not included in the current diagnostic guidelines [5] or have attempted to get at the core changes in social cognition and emotion processing. (Fig. 1). In addition, there has been the realisation that the effects of bvFTD are more widespread and affect physiological functioning.

Physiological Functioning

It is increasingly recognised that the changes in bvFTD are not simply restricted to behaviour, cognition and motor function, but that fundamental alterations in bodily functions including satiety and metabolism, as well as autonomic function occur. These changes have been linked to the disruption of large-scale neural networks linked to the hypothalamus with associated neuroendocrine changes [7].

Central to our understanding of physiological disturbances in bvFTD are changes in hypothalamic volume which have been shown in a number of neurodegenerative conditions including FTD and ALS [8], with abnormalities in eating and metabolism in bvFTD linked to potential connections between the hypothalamus and reward pathways [9]. Two studies have examined hypothalamic volumes in bvFTD. In the first, posterior hypothalamic atrophy was associated

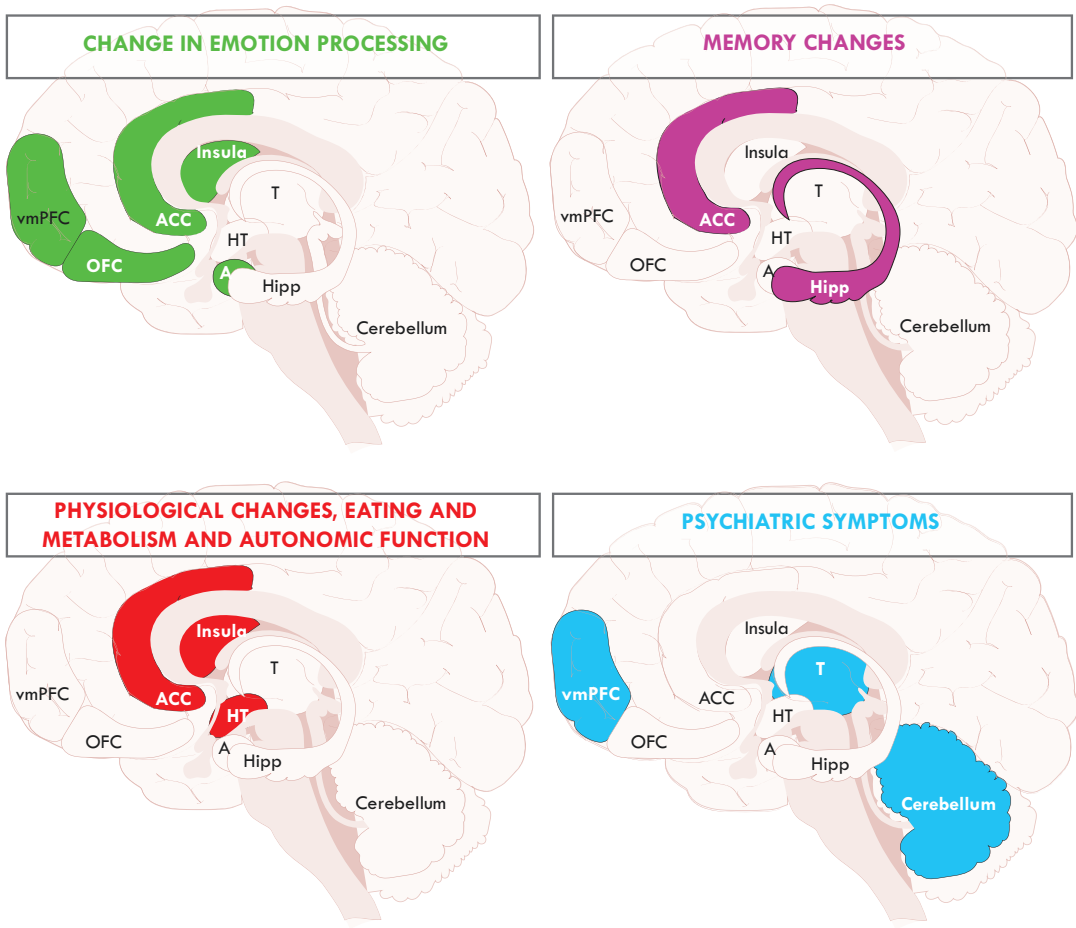

Fig. 1 Key neural structures implicated in each of the emerging symptom groups in bvFTD. (*vmPFC* ventral medial prefrontal cortex; *OFC* orbitofrontal cortex; *ACC* anterior cingulate cortex; *HT* hypothalamus; *T* thalamus; *Hipp* hippocampus; *A* amygdala)

with feeding abnormalities [10]. This relationship was observed within 2 years of disease onset, with continuing atrophy over the course of the disease. Importantly, atrophy was more pronounced in cases with transactive response DNA binding protein 43 kDa (TDP-43) inclusion pathology than in those with tau inclusions, pointing to a potential in vivo biomarker [10]. A second study reported a 17% reduction in hypothalamic volume on neuroimaging in bvFTD compared to controls, again particularly involving the posterior hypothalamus [11].

Eating and Metabolism in Behavioural Variant Frontotemporal Dementia

Hyperorality and dietary changes, which form one of the six core criteria for the diagnosis of bvFTD [5], are reported in over 60% of patients at initial presentation [12]. Such changes discriminate FTD from other dementias, notably Alzheimer's disease [13]. The changes in eating habits vary across the clinical subtypes of FTD. Alterations in bvFTD patients have been characterised by hyperphagia, indiscriminate eating, increased preference for sweet foods and other oral behaviours compared to patients with Alzheimer's disease [14]. In SD, changes are

also present but take a different flavour. In this syndrome, patients show prominent changes in food preference including increased selectivity and rigidity surrounding food consumption [14–16]. It has been suggested that this may be related to changes in knowledge about different foods [17].

Recently, ecologically valid methods, such as test meal approach used in obesity research to measure food intake, have been applied in FTD. When offered a test meal of breakfast after fasting, Ahmed and colleagues (2016) demonstrated a markedly increased total caloric intake in bvFTD patients compared to both AD and control subjects and a preference for sugar. In addition, they also revealed rigid eating behaviour and a strong sugar preference in SD patients [18]. A number of brain regions were found to be associated with abnormal eating behaviour. In bvFTD, consistent regions identified have been a distributed set of frontoinsular and anteromedial temporal brain areas [19, 20], which parallel those involved early in bvFTD [21, 22]. Increased caloric intake in bvFTD has also been related to atrophy of a network involving the bilateral anterior and posterior cingulate gyri, the thalamus, bilateral lateral occipital cortex, lingual gyri and the right cerebellum. These structures are also implicated in the control of cognitive reward, autonomic, neuroendocrine and visual modulation of eating behaviour [18]. Changes in eating behaviour have also been linked to hypothalamic atrophy and changes in key neuroendocrine peptides (Fig. 2) including agouti-related peptide, neuropeptide Y (NPY) and leptin [8, 23]. How hypothalamic changes and changes in neuroendocrine peptides control eating behaviour in bvFTD and interact with cortical networks controlling eating behaviour requires further investigation.

Given the prominent changes in eating behaviour in bvFTD, it is not surprising that patients also exhibit changes in metabolism including changes in body mass index (BMI), insulin and cholesterol levels. Both bvFTD and SD patients have modestly increased BMI and waist circumference compared to normal controls [16], although the degree of change is less than one might predict, given the level of eating abnormalities found in bvFTD, raising the question of whether other alterations in metabolic rate are present, similar to those seen in ALS [24], which may counteract some of the effects of these abnormal eating behaviours on BMI [20]. In keeping with this hypothesis, increased energy expenditure with a raised heart rate and autonomic changes have been shown in bvFTD [25] and have been correlated to atrophy in structures known to mediate autonomic function including the anterior cingulate cortex and insula.

Changes in insulin levels and lipid levels including insulin resistance have been identified in both bvFTD and SD with increased insulin and triglycerides and lower HDL cholesterol (reflecting a state of insulin resistance) [26]. Along the ALS-FTD spectrum, changes in lipid levels including increased cholesterol levels have been found to correlate with improved survival [27] and are mediated by changes in fat intake. Interestingly, these changes may occur decades before disease onset, suggesting a potential marker of disease [28]. The overall impact of these changes on disease progression and survival requires further exploration, including whether these changes are the result of atrophy in specific brain areas or actually modify the neurodegenerative process.

Autonomic Functions in Behavioural Variant Frontotemporal Dementia

In addition to changes in eating and metabolism, autonomic dysfunction has been identified in both bvFTD and SD [29]. Anecdotally, many carers report episodes of dizziness, as well as changes in thermoregulation in patients. Carer-based surveys have reported a high rate of symptoms related to blood pressure control, gastrointestinal function, thermoregulation, sweating and urinary symptoms [29, 30]. Objective measures of autonomic processing show abnormal responsiveness to emotion stimuli in FTD using physiological measures such as skin conductance [31, 32]. Changes in pain perception have been reported with bvFTD potentially associated with blunted pain and temperature responsiveness, while heightened

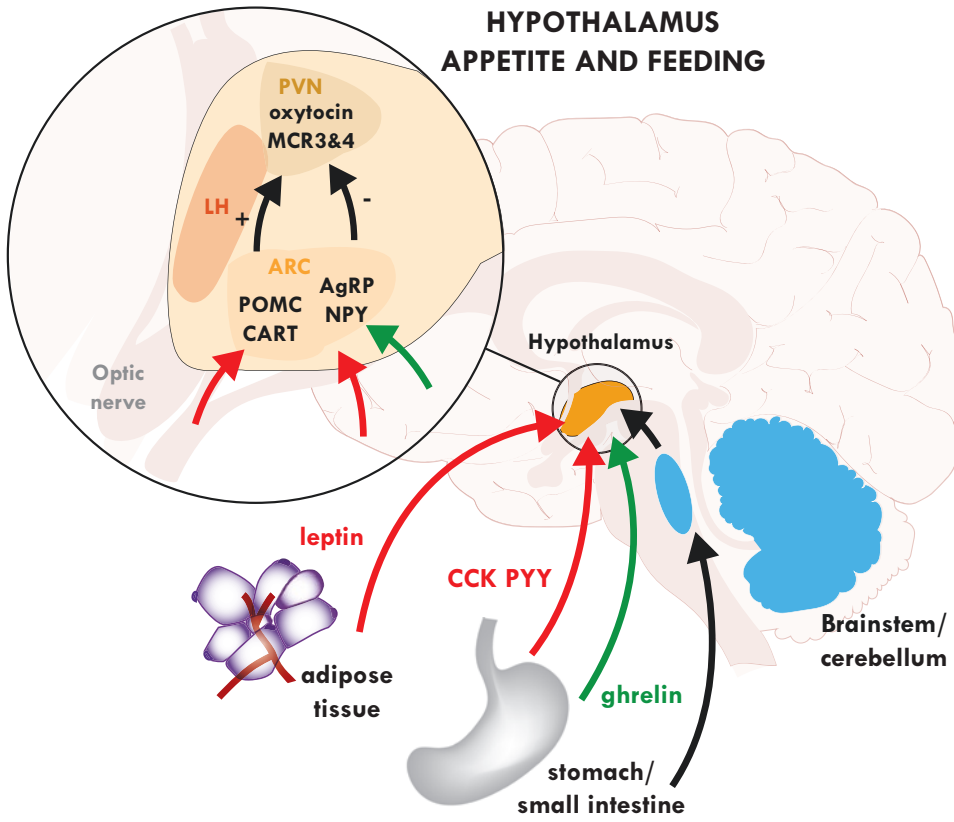

Fig. 2 Eating behaviour and the hypothalamus. Structures implicated in eating behaviour in FTD and pathways controlling eating behaviour in healthy individuals. Structures implicated in FTD include orbito-frontal cortex, right-sided reward structures including putamen, pallidum and striatum and posterior hypothalamus. Normal eating behaviour is controlled by an appetite stimulating pathway (shown in green) which results from ghrelin being released peripherally and targeting neurons of the arcuate nucleus (ARC) of the hypothalamus that contain neuropeptide Y (NPY) and agouti-related peptide (AgRP). An appetite suppressing pathway involves leptin (shown in red) being released from peripheral adipocytes, which then acts on pro-opiomelanocortin (POMC) and the cocaine and amphetamine-related transcript (CART) neurons in the hypothalamus. Peptide tyrosine tyrosine (PYY) and cholecystokinin (CCK), released peripherally, also suppress appetite. AgRp, NPY, POMC and CART neurons in the hypothalamus project to and act on melanocortin receptors (MCR). POMC is cleaved into alpha and beta-melanocyte-stimulating hormones that act on melanocortin receptor subtypes 3 and 4 (MCR 3 and 4) to decrease food intake. AgRP stimulates food intake by antagonism of MCR 3 and 4 receptors. In bvFTD, elevated levels of AgRP have been found. Increased leptin levels have also been found likely secondary to increased adipose stores. Autonomic pathways (black arrow) are also involved in food intake through projections via the brainstem and cerebellum to the hypothalamus. (*PVN* paraventricular nucleus)

responses are observed in SD and PNFA [33]. Recent studies using heart rate monitoring have shown increased heart rate and decreased heart rate variability in bvFTD [34]. Abnormalities in autonomic dilation of pupils in response to auditory stimuli are considered a physiological signature of neurodegeneration in FTD [35].

It is well established that autonomic changes may result from damage to cortical structures including the anterior and mid-cingulate cortices, prefrontal cortex, insula, ventral striatum, amygdala and hypothalamus [36, 37] regions known to undergo marked changes in FTD. Atrophy in the amygdala, ventral striatum, insula and anterior cingulate cortices has been reported in FTD [21,

36]. In bvFTD, pathological changes in these structures have traditionally being linked to disturbance of behaviour and social-emotional functioning [38–41]; however, their role in autonomic function has been recently investigated. Decreased cardiac vagal tone has been linked to left-lateralised structural frontoinsular and anterior cingulate cortex atrophy in FTD [34]. Atrophy in the premotor/anterior cingulate cortex and the putamen/claustrum/insula has been associated with urinary incontinence [42], while changes in the amygdala and insula have been linked to defective emotionally mediated autonomic dysfunction [43]. Pathology in the mesial temporal cortex, insula and amygdala is related to increased resting and sleeping heart rate [25]. The insula is also involved early in the course of bvFTD [21] and atrophy in this region correlates with altered pain and temperature perception [33], with the suggestion that the insula forms a network hub for sensory homeostatic signaling together with the thalamus [44]. Further research is required to examine how atrophy in these key regions regulates changes in autonomic function in FTD, how these changes are reflected in the different clinical phenotypes of FTD and how they could be harnessed as markers of disease progression.

Memory Function in Behavioural Variant Frontotemporal Dementia

Historically, memory functions have been reported to be preserved in bvFTD, with integrity of memory a key feature distinguishing Alzheimer's disease and bvFTD. Indeed, in clinical practice, it is not uncommon to read in clinical letters that a diagnosis of bvFTD is unlikely because the patient is exhibiting impaired memory function on cognitive testing. This position is further reflected in the consensus diagnostic criteria, where the cognitive profile in bvFTD (symptom F) is defined as one of executive/generation deficits, *with relative sparing of memory and visuospatial functions* [5]. Indeed, when present, memory deficit was thought to reflect a disturbance in retrieval efficiency, rather than a true episodic memory deficit, whereby information is encoded appropriately but recall performance is impaired because of an inability to retrieve efficiently and accurately the relevant information. Improvement in performance following the provision of cues (e.g. with recognition or forced-choice recognition formats) provides support for this position.

In the past decade, however, it has become increasingly apparent that various aspects of memory function can be severely affected in bvFTD, to a degree comparable to that seen in patients with Alzheimer's disease. Impaired performance is observed on common tasks of verbal and nonverbal episodic memory, such as short stories, word list learning or design recall, as well as on autobiographical memory and future thinking/prospective memory tasks [45–47], that correlates with the integrity of the hippocampus and other brain regions known to participate in memory functions [40, 48]. Deficits are also observed on tasks that rely on intact episodic and semantic memory systems, such as scene construction [49]. Further, evidence indicates that over time, episodic memory tends to worsen more rapidly in bvFTD than in AD [50]. Performance on topographical memory may, however, differentiate these two groups, where patients in AD tend to experience greater spatial orientation disturbance compared with patients with bvFTD [51].

Arguably, a differential diagnosis is not based solely on the presence/absence of a single clinical feature but is made within the context of multiple indices of clinical phenomenology, background and clinical history and ancillary investigations (e.g. brain MRI). Given the prominence of episodic memory deficit towards a clinical diagnosis of AD, it is important to emphasise that the presence of impaired memory, either on testing or clinical history, should not rule out a diagnosis of bvFTD.

Social Cognition in Behavioural Variant Frontotemporal Dementia

As its name indicates, disturbance in various aspects of social cognition is at the core of the prototypical presentation of bvFTD. In the current diagnostic criteria, these changes are covered by Symptom A (Early behavioural disinhibition) and Symptom C (Early loss of sympathy or empathy), both of which comprise additional subcategories. As is the case with the other symptoms, these symptom lack clear definitions, apart from the fact that they need to be persistent and recurrent, rather than one off or rare events [5]. Nearly 280 peer-reviewed articles have been published investigating social cognition in frontotemporal dementia to date. Of these, over 200 were published in the last decade, denoting the increasing interest in this topic. This should not come as a surprise for at least two reasons. First, social cognition forms a central block of interpersonal relationships. Humans are essentially social beings that have evolved because of their capacity to live in increasingly complex social environments. As such, disturbance in the capacity to engage or respond socially will have an impact not just for the affected individuals but for their broad social structure as well. In addition, evidence from epidemiological studies has shown that social interactions and social networks are protective risk factors against dementia in later life [52].

Second, the increasing availability of novel technologies in recent years, such as functional MRI, eye tracking or virtual reality, has opened the door to a variety of investigations, not possible until then, to understand the phenomenology of social cognition in healthy and clinical populations and their biological substrates (see for example [53] for a review). These investigations in healthy individuals and in clinical – stroke, tumour, neurodevelopmental and neurodegenerative – populations have identified a number of brain regions that play a central role in supporting social cognition. These regions are widespread and include frontal (anterior insula, anterior cingulate, orbitofrontal, medial frontal), temporal (temporal pole, superior temporal sulcus, amygdala) and parietal (temporo-parietal junction) brain regions [53–55].

Investigations in bvFTD have further confirmed the presence of pervasive changes in social cognition, which take many forms including emotion processing (recognition, expression), empathy, theory of mind, moral reasoning, reward sensitivity and understanding of social rules [32, 56–59]. These deficits can occur in isolation or in various combinations. Importantly, these findings suggest that single-test investigations of social cognition integrity are unlikely to be sufficient for ascertaining the presence of positive Symptoms A and C in the clinic.

While remarkable in its phenomenology and variability, the emergence of social cognition deficits in bvFTD is consistent with the pattern of brain atrophy observed in this syndrome. Indeed, the regions most susceptible to neuropathological changes and atrophy are the same that have consistently implicated in social cognition [60]. Importantly, these investigations have also identified that, in addition to brain atrophy, social cognition deficits also arise from global system disturbance, in particular in the autonomic system, leading to inaccurate integration of internal signals with external stimuli, resulting in inadequate or inappropriate responses [32, 61–63].

Importantly, the work of the past couple of decades has also demonstrated that disturbance in social cognition in FTD is not confined to its behavioural variant. Indeed, although beyond the scope of this chapter, it is important to note the emergence of such deficits in the language presentations of FTD, semantic dementia and progressive nonfluent aphasia. The characteristics of these deficits appear to differ from those in bvFTD, in their severity and quality. As such, and similar to what was discussed in the memory section, disturbance of social cognition capacity in the presence of a co-existing language disturbance should not necessarily rule out a diagnosis of language variant of FTD.

Overlap of Behavioural Variant Frontotemporal Dementia and Psychiatric Conditions

The current diagnostic criteria for bvFTD state that behavioural disturbances may not be better explained by a psychiatric condition [5]. The early clinical diagnosis of bvFTD, however, is often made difficult by the overlap with late onset psychiatric conditions. Patients often initially present with apathy and inertia and changes in empathy, which is mistakenly diagnosed as late onset depression. Not uncommonly, patients are placed on anti-psychotic medication, which can lead to changes in eating behaviour and weight gain, often blurring the presence of hyperorality changes. Once patients develop the florid behavioural changes including psychotic features, obsessive compulsive features, they are often misdiagnosed as schizophrenia, schizoaffective disorder or bipolar disorder [64].

Compounding the overlap between bvfTD and psychiatric conditions is the finding of high rates of psychiatric features in bvFTD patients with the chromosome 9 open reading frame 72 (*C9orf72*) gene expansion and the fact that such symptoms may be present for many years before the emergence of more characteristic FTD features. In a recent study of 56 bvFTD cases [65], a third showed psychotic features, with *C9orf72* expansion cases more likely to exhibit psychotic symptoms than non-carriers (64% vs. 26%). Delusions, which comprise of persecutory, somatic, jealous and grandiose types, were more likely to occur in *C9orf72* expansion carriers (57% vs. 19%), as were hallucinations (36% vs. 17%). Increased psychotic symptoms in *C9orf72* expansion carriers correlated with atrophy in a distributed cortical and subcortical network that included discrete regions of the frontal, temporal and occipital cortices, as well as the thalamus, striatum and cerebellum. These structures are similar to structures involved in psychiatric conditions such as schizophrenia [65]. The situation is further confounded by the findings of a large study of 1414 family members of patients with bvFTD that found that relatives of patients with the *C9orf72* gene expansion have an increased incidence of young onset schizophrenia and autism spectrum disorder [66]. Further research is needed to understand the overlap between bvFTD and psychiatric conditions and predisposition to psychiatric conditions as this may aid in earlier detection and treatment targeting.

Behavioural Variant Frontotemporal Dementia Phenocopy Syndrome

Along the bvFTD-psychiatric spectrum are patients that initially present with behavioural and neuropsychiatric features; yet, they do not show frontotemporal atrophy or hypometabolism on imaging and do not progress to develop cognitive decline or functional impairment [67]. It has been proposed that these patients may represent a late onset decompensation of life-long personality disorders or a neuropsychiatric condition, rather than true bvFTD [68]. Two patients with this disorder that went to autopsy showed no evidence of FTD pathology [69]. Caution, however, should be taken when classifying patients with the phenocopy syndrome in the absence of genetic testing for the *C9orf72* gene expansion. Indeed, a recent meta-analysis on the phenocopy syndrome reported 7 cases of slowly progressive FTD that were associated with the *C9orf72* gene expansion, out of a total of 292 reported phenocopy cases [67]. This finding is in keeping with a very long-term follow up of 16 cases from Cambridge, UK, all of whom were tested for the *C9orf72* gene expansion found in 1 case only (6.25%). Reports showing the phenotypic variability in patients with the *C9orf72* gene expansion are also increasing, with reports of patients within the same family having a rapid course in their 40s and death within 3 years and a much more indolent course in their 70s [70]. Further studies are required to ascertain the difference in penetrance and the underlying pathological mechanisms responsible for this. Studies of the effect of repeat size have produced discordant findings, and the contribution of repeat size to penetrance and phenotype remain uncertain and require further investigation [71–73].

Current Areas of Research Development

Amyotrophic Lateral Sclerosis: Frontotemporal Dementia Overlap

Since the mid-2000s, FTD and amyotrophic lateral sclerosis (ALS) have been increasingly conceptualised as representing the opposite ends of a disease spectrum [74, 75], with mounting evidence pointing towards an aetiological overlap between ALS and FTD and a multitude of studies showing behavioural and cognitive changes across the spectrum [27, 76–78]. This has largely been driven by genetics, with the discovery of the *C9orf72* expansion causing both bvFTD and ALS [79, 80]. In contrast to FTD, patients diagnosed with ALS typically exhibit limb or bulbar symptoms at initial presentation [81–83]. Much debate continues over the incidence of cognitive changes in ALS (behavioural, cognitive, language), with most large and community-based surveys reporting some cognitive changes in around 40–50% of cases [84, 85], while up to 15% of patients may satisfy the criteria for a diagnosis of concomitant FTD [86]. Conversely, 10–15% of FTD patients develop ALS, with varying estimates of motor neuron dysfunction in FTD insufficient to reach criteria for ALS, at between 25% and 30% [74, 87]. Further confirmation of the aetiological overlap between FTD and ALS is the finding of TDP-43 pathology in virtually all ALS cases and around half of those with bvFTD, although only 25% of bvFTD patients have similar motor neuron-like neuronal TDP-43 inclusion pathology [88, 89].

Recent research has suggested that bvFTD and ALS with TDP-43 inclusions may potentially result from the regional spreading ('prion like') of TDP-43 in the brain and spinal cord [90–92], with different initiating regions of pathology involved. In ALS, the pathology begins in the motor neocortex, progressing rapidly to the spinal cord and brainstem, prior to the involvement of nearby frontal and parietal regions, and then finally involving the temporal lobes [93]. Such a pattern of spread may potentially explain the late development of cognitive symptoms in ALS. In bvFTD, the disease process is thought to begin in the frontal lobe prior to spreading into the premotor, primary motor, parietal and temporal cortices, and eventually into the spinal cord [94].

In contrast to a suggested spectrum of disease, recent evidence indicates that the overlap between ALS and FTD is far more complex [95], with debate focusing on the cognitive and behavioural differences between ALS-FTD and bvFTD (i.e. are ALS-FTD and bvFTD part of the same disease). Previous studies have shown greater language involvement in ALS-FTD than in bvFTD [96, 97] including reduced sentence comprehension and grammatical difficulties with a language presentation of ALS-FTD with progressive nonfluent aphasia associated with anterior temporal and frontal language area atrophy, while that with prominent semantic problems is associated with temporal lobe and orbitofrontal cortex atrophy [98]. Currently, many studies are focusing on the longitudinal progression of behavioural and cognitive changes in ALS and ALS-FTD. These will help delineate the true nature of the progression and allow us to better clinically phenotype patients, which will aid in clinical trial development.

Predictors of Clinical Progression

One of the most common questions asked in clinical practice is 'how will bvFTD progress' and 'what is a patient's predicted survival'. Longitudinal large-scale follow-up studies of bvFTD patients are limited, but a number of cohort studies including genetic mutation carriers are currently underway around the world. Patients with combined ALS-FTD tend to show more rapid progression to death than those with either pure ALS or bvFTD [99]. It has also been shown that survival in those with both ALS and FTD may be dependent on initial phenotypic presentation, with those with initial motor symptoms having a shorter survival than those with initial cognitive or behavioural symptoms [100]. A recent study examined predictors of progression and survival in a cohort of 75 bvFTD patients. Median survival time from disease onset was

10.8 years and median survival prior to transition to nursing home was 8.9 years. Shorter survival was predicted by shorter disease duration at presentation, greater atrophy in the anterior cingulate cortex, older age and a higher burden of behavioural symptoms. In terms of disease progression, presence of a known pathogenic frontotemporal dementia genetic mutation was the strongest predictor of progression. Deficits in letter fluency and greater atrophy in the motor cortex were also associated with faster progression [101]. Research is now focusing on variables that can aid in early diagnosis including potential markers that develop prior to cognitive change to aid in early diagnosis. These aspects have particularly focused on imaging analyses including examining cerebral blood flow patterns [102], showing abnormalities up to 12 years prior to disease onset and grey matter atrophy patterns between those affected mutation carriers and asymptomatic mutation carriers, with different atrophy patterns visible presymptomatically, between *C9orf72, MAPT* and *GRN* genetic abnormality carriers, but also a common network of atrophy involving the insula, orbitofrontal lobe and anterior cingulate cortex [103]. As discussed above, these regions potentially mediate a number of physiological changes, potentially offering potential physiological markers that could be developed to facilitate earlier diagnosis and monitoring of disease progression.

Treatment and Intervention

Disease-modifying treatments do not currently exist for FTD and recent efforts have yielded disappointing results, for example the double-blind, placebo-controlled trial of LMTM (leuco-methylthioninium bis(hydromethanesulphonate)), a derivative of methylthioninium chloride, a drug targeting tau protein aggregation, in bvFTD [104]. A few clinical trials are, however, in the pipeline, but mostly targeting the familial forms of the disease or symptomatic management (see clinicaltrials.gov). Drugs used in Alzheimer's disease, such as acetylcholinesterase inhibitors, or NMDA receptor antagonists, provide no benefits to bvFTD patients and may even have a negative impact on cognition. Similarly, symptomatic treatments of challenging behaviours (e.g. disinhibition, agitation, aggression) with selective serotonin reuptake inhibitors (SSRIs) or antipsychotics have had mixed results.

A number of non-pharmacological approaches targeting behavioural difficulties, such as apathy or aggression have shown promise. For example, a subset of patients will develop repetitive behaviours over time (e.g. lining up objects, jigsaw puzzles), which can negatively impact on the patient's level of independence and interpersonal relationship. Interventions, such as the Tailored Activities Program (TAP), that directly target a specific behaviour and redirect it into personalised and relevant activities (selected by the carer) have demonstrated positive results, in reducing the disruption associated with the behaviour, increased meaningful activity engagement and reduction in carer stress [105]. Unlike in mild cognitive impairment and in Alzheimer's disease, targeted cognitive retraining has not been widely investigated in bvFTD and its suitability remains to be established. The prominent and early lack of insight, common in this population, complicates direct patient interventions [106], and carer-based interventions may therefore be more suitable.

Supporting families by providing education and coping skills is an avenue with demonstrated success in other clinical populations, such as traumatic brain injury [107]. A pilot study in FTD reported positive findings, but these will need to be replicated on a larger scale to determine their applicability in FTD [108].

Concluding Remarks

It is clear that much has been learnt about bvFTD. In this review, we focus on topics which have been of particular interest to FRONTIER, our frontotemporal dementia clinical research group based in Sydney, Australia. We have shown that the effects of bvFTD extend to fundamental aspects of physiology and metabolism, and that, contrary to clinical opinion, episodic memory is

affected in bvFTD and reflects involvement of the hippocampus. Work on social cognition has emphasised the importance of breakdown in interpreting and expressing emotions, while the overlap between psychiatric disorders and bvFTD has been brought into focus by the finding of high rates of psychotic features in carriers of the *C9orf72* gene expansion and of psychiatric disorders in their family members. We have progressed knowledge on predictors of rapid versus slow decline in bvFTD, yet the holy grail for all researchers in the field – an effective therapy which can modify the clinical course of FTD – still remains beyond our grasp. We will certainly be ready when it comes, and there is some hope given the raft of new drugs under development, at least for use in those with known gene abnormalities who are still symptom free.

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The Neuropsychiatric Features of Behavioral Variant Frontotemporal Dementia

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Introduction

Frontotemporal dementia (FTD) is a clinically and neuropathologically heterogenous neurodegenerative disorder characterized by disturbances in behavior, personality, and language associated with degeneration of frontal and temporal brain regions [1]. FTD consists of three clinical variants distinguished by the predominant presenting symptoms: behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent/agrammatic variant primary progressive aphasia (nfvPPA) [2, 3]. Additionally, there are several related disorders which share features with FTD, including FTD with motor neuron disease (FTD-MND), corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP).

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Behavioral variant FTD is the most common form of FTD and comprises over 50% of all FTD cases [4]. The syndrome has an early age of onset with a mean of 58 years of age. The time between disease onset and the initial evaluation is approximately 3 years and the duration of the illness is approximately 8 years [2]. Behavioral variant FTD is characterized by a set of core diagnostic criteria proposed by Rascovsky et al. in 2011, which include behavioral disinhibition; apathy or inertia; loss of sympathy or empathy; perseverative, stereotyped, or compulsive/ritualistic behavior; hyperorality; and executive dysfunction (Table 1) [2]. All but one of these criteria (executive dysfunction) are behavioral in nature and have overlapping features with many psychiatric syndromes, including schizophrenia, obsessive-compulsive disorder (OCD), bipolar disorder (BPD) and major depressive disorder (MDD). Not surprisingly, many patients with bvFTD are mistakenly diagnosed with a primary psychiatric condition [5].

The neuroanatomical correlates of bvFTD typically show a pattern of atrophy in the frontal and anterior temporal lobes, with the right hemisphere being predominately affected. The earliest structures involved include the anterior cingulate cortex (ACC), anterior insula (AI), and orbitofrontal cortex (OFC). As the disease progresses, atrophy is found in the dorsolateral prefrontal cortex (dlPFC), frontal poles, dorsal insula (DI), striatum, thalamus, and anterior hippocampus. In later stages of the disease, atrophy becomes more

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Table 1 International consensus criteria for behavioral variant frontotemporal dementia

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD:

A. Shows progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant)

II. Possible bvFTD

Three of the following behavioral/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent rather than single or rare events

A. Early* behavioral disinhibition (one of the following symptoms [A.1–A.3] must be present):

A.1. Socially inappropriate behavior

A.2. Loss of manners or decorum

A.3. Impulsive, rash, or careless actions

B. Early apathy or inertia (one of the following symptoms [B.1–B.2] must be present):

B.1. Apathy

B.2. Inertia

C. Early loss of sympathy or empathy (one of the following symptoms [C.1–C.2] must be present):

C.1. Diminished response to other people's needs and feelings

C.2. Diminished social interest, interrelatedness, or personal warmth

D. Early perseverative, stereotyped, or compulsive/ritualistic behavior (one of the following symptoms [D.1–D.3] must be present):

D.1. Simple repetitive movements

D.2. Complex, compulsive, or ritualistic behaviors

D.3. Stereotypy of speech

E. Hyperorality and dietary changes (one of the following symptoms [E.1–E.3] must be present):

E.1. Altered food preferences

E.2. Binge eating, increased consumption of alcohol or cigarettes

E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of the following symptoms [F.1–F.3] must be present):

F.1. Deficits in executive tasks

F.2. Relative sparing of episodic memory

F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria.

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or as evidenced by clinical dementia rating scale or functional activities questionnaire scores)

C. Imaging results consistent with bvFTD (one of the following [C.1–C.2] must be present):

C.1. Frontal and/or anterior temporal atrophy on MRI or CT

C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioral variant FTD with definite FTLD pathology

Criterion A and either criterion B or C must be present to meet criteria:

A. Meets criteria for possible or probable bvFTD

B. Histopathological evidence of FTLD on biopsy or at postmortem

C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD

A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders

B. Behavioral disturbance is better accounted for by a psychiatric diagnosis

C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative processes

*As a general guideline 'early' refers to symptom presentation within the first 3 years. Adapted from Rascovsky et al. [2]. Used with permission

widespread and involves the posterior hippocampi, posterior insula (PI), and parietal lobes, regions that are prominently involved in Alzheimer's disease (AD) [6]. For that reason, in the late stages of bvFTD, there is considerable overlap with AD.

Neuropsychiatric Features of bvFTD

The bvFTD syndrome has substantial overlap with the symptomology of multiple primary psychiatric conditions, which presents a significant diagnostic challenge for clinicians. The difficulty in diagnostic accuracy is delineated in a study by Woolley et al. [5], who performed a systematic, retrospective, blinded chart review of 252 patients at the University of California, San Francisco Memory and Aging Center in order to identify the rate of psychiatric diagnoses which precede that of a neurodegenerative disorder. Of this population, 71 patients (28.2%) received a psychiatric diagnosis prior to ultimately being diagnosed with a neurodegenerative disorder, and approximately 50% with bvFTD were first diagnosed with a primary psychiatric disorder [5]. This study highlights the importance of understanding the key features of bvFTD in order to make an accurate diagnosis.

In this section, we will outline the neuropsychiatric features of bvFTD followed by a brief review of the overlap between bvFTD and primary psychiatric conditions, namely, MDD and BPD.

Disinhibition

Disinhibition is an early symptom of bvFTD and is present in 76% of cases at the time of the initial evaluation [2]. Disinhibition is often the most salient feature of bvFTD as patients frequently exhibit impulsivity, socially inappropriate behavior, and loss of social decorum attributable to aberrant reward processing and a lack of regard for potential consequences of inappropriate actions [2, 7, 8].

The most common manifestation of behavioral disinhibition is impulsivity [9], such as new-onset gambling or substance use, excessive spending, reckless behavior, or oversharing of personal information [2, 9, 10]. Violation of social norms often includes overfamiliarity, inappropriate touching, and inappropriate sexual acts [2, 11, 12]. Additionally, criminal behaviors occur in approximately 50% of cases [13]. A general lack of etiquette may be demonstrated by inappropriate laughing at a serious event, touching others, unbridled profanity, or making offensive jokes [2, 12].

Studies exploring the neuroanatomical correlates of disinhibition have largely implicated dysfunction of the right subgenual cingulate cortex (SGC) and the posteromedial aspect of the right OFC [14–16]. In addition to SGC and OFC involvement, Franceschi et al. also found that the bilateral inferior temporal cortex, hippocampus, amygdala, and nucleus accumbens were hypometabolic on fluorodeoxyglucose positron emission tomography (FDG-PET) in those with bvFTD who predominately exhibited disinhibition [15].

Sturm et al. found that atrophy of the right pregenual ACC in subjects with bvFTD was associated with a lower degree of self-conscious emotional reactivity [17], which suggests that this brain region may play a role in disinhibited behavior. In another study, Perry et al. found that the inability of participants to subjectively differentiate between pleasant and unpleasant odors was correlated with atrophy of the right ventral mid-insula and right amygdala, suggesting that the lack of aversion to negative stimuli may be a component of reward-seeking behavior seen in those with disinhibited behavior [8].

Pharmacological treatments targeting disinhibited behavior are limited, though some studies demonstrate that selective serotonin reuptake inhibitors (SSRI) may be effective. In a small open-label study by Swartz et al., 11 subjects with FTD were treated with fluoxetine, sertraline, or paroxetine for three months and were found to have a reduction in the degree of disinhibition [18]. In another open-label study by Herrmann et al., 15 subjects with FTD were treated with citalopram 30 mg daily for six weeks and were found to have significant decreases on the neuropsychiatric inventory (NPI) questionnaire total score and on the disinhibition subscore of the NPI [19].

Apathy

Apathy is the most common presenting symptom of bvFTD, occurring in 84% of cases at the time of the initial evaluation [2]. It is characterized by the reduction of goal-directed behavior, diminished emotional reactivity, and a decrease in social engagement [20]. Apathy initially manifests as a reduction of spontaneous activity and a general sense of indifference [20–22]. In later stages of the disease process, apathy may result in substantial functional impairment with limited ability to perform instrumental and basic activities of daily living (ADL) [23]. The functional impairment resulting from apathy is often very difficult for those caring for the patient and can lead to substantial emotional distress [24].

A diagnostic framework for the diagnosis of apathy was proposed by Marin in 1991 [21]. Marin described apathy as a distinct neuropsychiatric syndrome defined by a lack of motivation, a decrease in goal-directed behavior, and a loss of interest [21]. Despite Marin's proposed diagnostic criteria describing the apathy syndrome, the concept of apathy has varied throughout the literature leading to confusion due to lack of a formal definition. Levy and Dubois defined apathy as a "quantitative reduction of voluntary, goal-directed behaviors" and defined three subtypes, emotional-affective, cognitive, and autoactivation. This definition was important for delineating three different behavioral syndromes associated with three different anatomical correlates [25]. A more recent set of diagnostic criteria describing the apathy syndrome has been proposed by a consensus panel of 23 experts (Table 2) in order to formally define the concept of apathy [20, 22].

The neuroanatomical correlates of apathy in those with bvFTD have been largely associated with dysfunction of the frontal lobes. Studies utilizing voxel-based morphometry (VBM) demonstrate predominately right-sided atrophy of the medial prefrontal cortex (mPFC) [14, 16, 26] and the ACC [14, 16, 26, 27]. Other areas of involvement include the dlPFC [16, 26], OFC [14, 16, 27], insula [26, 28], and the caudate [28].

Pharmacological treatments targeting apathy are limited. Psychostimulants may result in

Table 2 Apathy diagnostic criteria

Criterion A: A quantitative reduction of goal-directed activity either in behavioral, cognitive, emotional, or social dimensions in comparison to the patient's previous level of functioning in these areas. These changes may be reported by the patient himself/herself or by observation of others
Criterion B: The presence of at least two of the three following dimensions for a period of at least four weeks and present most of the time:
B1. Behavior and cognition Loss of, or diminished, goal-directed behavior or cognitive activity as evidenced by at least one of the following:
General level of activity: The patient has a reduced level of activity either at home or work, makes less effort to initiate or accomplish tasks spontaneously, or needs to be prompted to perform them **Persistence of activity:** He/she is less persistent in maintaining an activity or conversation, finding solutions to problems, or thinking of alternative ways to accomplish them if they become difficult **Making choices:** He/she has less interest or takes longer to make choices when different alternatives exist (e.g., selecting TV programs, preparing meals, choosing from a menu, etc.) **Interest in external issue:** He/she has less interest in or reacts less to news, either good or bad, or has less interest in doing new things **Personal well-being:** He/she is less interested in his/her own health and well-being or personal image (general appearance, grooming, clothes, etc.)
B2. Emotion Loss of, or diminished, emotion as evidenced by at least one of the following:
Spontaneous emotions: The patient shows less spontaneous (self-generated) emotions regarding their own affairs or appears less interested in events that should matter to him/her or to people that he/she knows well **Emotional reactions to environment:** He/she expresses less emotional reaction in response to positive or negative events in his/her environment that affect him/her or people he/she knows well (e.g., when things go well or bad, responding to jokes or events on a TV program or a movie, or when disturbed or prompted to do things he/she would prefer not to do) **Impact on others:** He/she is less concerned about the impact of his/her actions or feelings on the people around him/her **Empathy:** He/she shows less empathy to the emotions or feelings of others (e.g., becoming happy or sad when someone is happy or sad or being moved when others need help) **Verbal or physical expressions:** He/she shows less verbal or physical reactions that reveal his/her emotional states

(continued)

Table 2 (continued)

B3. Social interaction Loss of, or diminished, engagement in social interaction as evidenced by at least one of the following:
Spontaneous social initiative: The patient takes less initiative in spontaneously proposing social or leisure activities to family or others **Environmentally stimulated social interaction:** He/she participates less or is less comfortable or more indifferent to social or leisure activities suggested by people around him/her **Relationship with family members:** He/she shows less interest in family members (e.g., to know what is happening to them, to meet them or make arrangements to contact them) **Verbal interaction:** He/she is less likely to initiate a conversation, or he/she withdraws soon from it **Homebound:** He/she prefers to stays at home more frequently or longer than usual and shows less interest in getting out to meet people
Criterion C: These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning
Criterion D: The symptoms (A–B) are not exclusively explained or due to physical disabilities (e.g., blindness and loss of hearing), to motor disabilities, to a diminished level of consciousness, to the direct physiological effects of a substance (e.g., drug of abuse, medication), or to major changes in the patient's environment

Adapted from Robert et al., 2018 [20]. Used with permission

some improvement, though careful patient selection is essential due to the potential for significant side effects, including insomnia, hypertension, irritability, and psychosis. Methylphenidate has shown benefit in multiple small studies [29]. In several randomized controlled trials (RCT), methylphenidate was associated with significant improvement in apathy in those with AD [30, 31, 32]. One small RCT of eight patients diagnosed with bvFTD found that treatment with dextroamphetamine resulted in an improvement in neuropsychiatric inventory (NPI) subscales of apathy by 2.8 points [33]. Despite some improvement in symptoms, these small studies do not justify treating FTD with stimulants in most cases given the potential for significant adverse events.

Loss of Empathy or Sympathy

Loss of empathy is a presenting symptom in 73% of bvFTD cases [2]. Symptoms manifest as emotional detachment and a decrease in social interest, as well as a lack of concern for the feelings of others [2, 34]. This indifference can profoundly impact relationships early in the disease course and often results in substantial caregiver burden by disruption the emotional connection between the caregiver, often the patient's spouse, and the patient [35, 36]. In extreme cases, lack of empathy may manifest as sociopathic behavior [37]. When coupled with disinhibition and impulsivity commonly demonstrated by those with bvFTD, loss of empathy may lead to criminal behavior, ranging from petty theft to homicide [38].

Empathy is a complex construct in which an observer is able to identify with the feelings, thoughts, or emotions of another individual, leading to a change in the observer's affective state [39]. The ability to empathize is a fundamental aspect of social interaction and involves affective perspective taking and affect sharing [39]. The affective perspective taking and affect sharing of empathy are broken down into cognitive components and affective components, each of which has multiple subcomponents that are beyond the scope of this chapter [40, 41]. The cognitive components of empathy involve the observer understanding what others may be thinking or feeling, while the affective components involve sharing and responding to the emotional experience of others [40]. This paradigm allows for a better understanding of the empathy deficits demonstrated in bvFTD.

The underlying neuroanatomy implicated in the loss of empathy is largely related to the widespread dysfunction of structures that are associated with both cognitive and affective empathy. A lesional study by Shamay-Tsoory et al. demonstrated that cognitive empathy and affective empathy were associated with distinct neuroanatomical substrates. Deficits in cognitive empathy were found to be associated with lesions of the right ventromedial PFC (vmPFC), while deficits in affective empathy were found to be associated with lesions of the left inferior frontal gyrus (IFG)

[42]. A by Dermody et al. in subjects with bvFTD correlated well with the earlier study by Shamay-Tsoory et al. Dermody et al. found that the diminished cognitive empathy in bvFTD was associated with predominately right-sided atrophy of the mPFC, OFC, insular cortices, and lateral temporal lobes. Diminished affective empathy was associated with predominately left-sided atrophy of the OFC, (IFG), insula, thalamus, putamen, and the bilateral mid-cingulate gyrus [43].

Pharmacological treatments targeting loss of empathy in bvFTD are limited, though studies evaluating the therapeutic effects of oxytocin have shown positive results. Hurlemann et al. assessed the effect of intranasal oxytocin in a randomized, double-blind, placebo-controlled trial of 48 healthy male volunteers and demonstrated that intranasal oxytocin enhanced emotional empathy but not cognitive empathy [44]. Subsequent randomized, double-blind, placebo-controlled trials regarding the effects of oxytocin were performed by Jesso et al. (n = 20) and Finger et al. (n = 46) in subjects with bvFTD. Both studies demonstrated significant improvement in measures of empathy [45, 46].

Perseverative, Stereotyped, or Compulsive/Ritualistic Behaviors

Repetitive behaviors occur in bvFTD at the time of initial evaluation in 71% of cases [2] and may be related to deficits in suppressing urges to perform an action [47]. These behaviors can present as simple repetitive movements or vocalizations, such as eye blinking, throat clearing, or tapping, among others. More complex behaviors are also frequently observed, including collecting and hoarding behavior, repetitive storytelling, and frequent unnecessary trips to the bathroom [2, 48, 49, 50].

Some of the repetitive behaviors seen in bvFTD have features related to deficits in impulse control. Compulsions, as typically seen in OCD, are characterized in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as purposeful repetitive motor acts that are associated with obsessive thoughts and performed to reduce anxiety or distress [51]. In those with OCD, performing the behavior results in relief from distress, though the action is not intrinsically pleasurable [52, 53]. In contrast to that seen in OCD, impulsivity typically seen in bvFTD is characterized by the inability to resist urges due to deficits in response inhibition and delayed gratification, as well as a lack of consideration for potential consequences. This leads to an act performed due to the need to immediately satisfy a desire rather than to alleviate anxiety or distress [54, 55]. In a study by Moheb et al., it was demonstrated that typical repetitive behaviors seen in bvFTD were complex and included stereotypic speech, hoarding, and frequent unnecessary trips to the restroom. In contrast, symptoms typical of OCD, such as checking, counting, and ordering, were infrequent. Furthermore, repetitive behaviors in bvFTD were not associated with anxiety, and were able to be stopped on command without causing distress [50]. In contrast to the study by Moheb et al., other studies have found that symptoms typical of OCD are prominent in bvFTD [47, 56, 57, 58].

The neuroanatomical correlates of repetitive behaviors in bvFTD are largely related to the dysfunction of structures in the left temporal lobe and striatum. A study by Rosso et al. performed computed tomography (CT) and/or MRI on 87 subjects and found that left temporal lobe atrophy was associated with complex compulsive behaviors, which included preoccupation with ideas or activities, strict adherence to a fixed schedule, frugality, arranging items in a particular order, and cleaning rituals [59]. Similarities were found in a functional imaging study using single-photon emission computed tomography (SPECT), which correlated hypoperfusion of the left temporal lobe with compulsive behavior, and hypoperfusion of the right frontal lobe with stereotypical behavior [60]. The role of the striatum in stereotypical behavior associated with bvFTD was further described in a study utilizing VBM by Josephs et al., who demonstrated disproportionate atrophy of the putamen and caudate head bilaterally [61]. Additionally, atrophy of the dorsal ACC and right supplementary motor area was found to be associated with repetitive behavior in a study by Rosen et al. [14]

The pharmacological treatments specifically targeting repetitive behaviors in those with bvFTD are limited, though some studies have demonstrated modest improvement in symptoms. In a small open-label study published by Swartz et al., previously described in this chapter, a reduction in compulsive behaviors was noted after treatment with an SSRI [18]. A case series of three patients reported improvement in compulsive behavior associated with bvFTD with the use of clomipramine [62]. A case report indicated that topiramate was effective in helping to reduce alcohol use in an individual with bvFTD [63]. Lastly, a small study by Mendez et al. found that those with FTD who were treated with donepezil were more likely to experience worsening of disinhibition and compulsive behavior, which returned to baseline after donepezil was discontinued [64].

Hyperorality and Dietary Changes

Hyperorality and dietary changes have long been recognized as a feature of neurodegenerative disease [65] and have been considered a core feature of bvFTD since the diagnostic criteria proposed in 1998 by Neary et al. [66]. Significant changes in eating behavior are present in 59% of those with bvFTD at the initial evaluation [2] and increase with the progression of disease [67]. A range of disordered eating behavior has been described, including increased appetite, excessive eating regardless of satiety, alterations in food preferences often with a preference for carbohydrates, and, in severe cases, oral exploration, chewing, or ingestion of inedible objects [2, 68, 69, 70]. The potential degree of insatiability that may be seen in those with bvFTD was clearly demonstrated in a study by Woolley et al., where participants were given sandwiches for lunch and allowed to eat as many as they wished for up to one hour. Sandwiches were continuously brought to the participants, regardless of their requests, in order to maintain a constant volume of sandwiches in front of the participant. Those with bvFTD were much more likely to eat more sandwiches than controls. In some cases, participants with bvFTD requested that sandwiches stop being brought to them, despite continuing to eat the sandwiches [70].

The underlying neuroanatomical correlates of eating behavior are likely multifactorial, though multiple studies have implicated orbitofrontal-insular-striatal networks as a mediator of eating behavior and satiety [70, 71, 72]. A study by Woolley et al. utilizing VBM demonstrated that atrophy of the right ventral insular cortex, striatum, and anterior OFC was associated with increased food consumption [70]. A similar study by Whitwell et al. demonstrated that increased food consumption was associated with atrophy of the anterolateral OFC bilaterally [71]. Whitwell et al. correlated the increase in carbohydrate craving associated with bvFTD with the right AI and the posterolateral OFC bilaterally [71]. There is also evidence that changes in the hypothalamus may lead to disturbance in eating behavior. In a study by Piguet et al., significant atrophy of the hypothalamus was present on structural MRI as well as on postmortem analyses in patients with bvFTD who demonstrated a significant disturbance in eating behavior [72].

Treatment modalities targeting hyperorality and dietary changes are limited, though there have been a small number of medications that have resulted in improvement. Serotonergic medications are the most widely studied in bvFTD. In a small open-label study performed by Swartz et al., previously described in this chapter, treatment with an SSRI resulted in a decrease in carbohydrate craving [18]. Additional studies found that fluvoxamine and trazodone were also effective at improving eating behaviors [73–75]. Given the limited number of available pharmacological treatment options, close caregiver supervision is often necessary in order to mitigate the potential for overeating, weight gain, and possible attempts to ingest inedible objects [11].

Overlapping Characteristics of bvFTD and Psychiatric Disorders

Neurodegenerative disorders, particularly bvFTD, and primary psychiatric disorders have many features in common, which presents a significant

diagnostic challenge for clinicans. Recognizing these overlapping features is an essential first step in uncovering the etiology of the patient's presenting symptoms. A thorough evaluation, including an exhaustive history, neuroimaging, and neuropsychological testing, can aid in narrowing the differential diagnoses and may result in findings that would have otherwise be missed, such as severe executive dysfunction noted on neuropsychological testing or frontotemporal atrophy demonstrated on MRI of the brain. In this section, we will briefly discuss some of the similarities between bvFTD, MDD, and BPD.

Overlapping Symptomatology

Early symptoms of bvFTD can mimic those found in late-life primary mood disorders, and are often experienced by those with MDD and BPD [5].

Major depressive disorder is a common psychiatric disorder characterized by intermittent episodes of depressed mood with several clinical features with bvFTD, which can potentially congtribute to diagnostic uncertainty, particularly in complicated or atypical cases. The diagnostic criteria for MDD are defined in DSM-5 by nine characteristic features: (1) depressed mood, (2) diminished interest or pleasure in activities, (3) a significant change in weight or appetite, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or guilt, (8) diminished concentration, and (9) recurrent thoughts of death or suicide [51]. Anhedonia is often present in those with MDD, though it can appear very similar to that of apathy associated with bvFTD as both often present clinically as decreased motivation. In this case, other symptoms would likely aid in clarifying the underlying diagnosis, however, differentiating bvFTD and MDD can become increasingly difficult in those with atypical or severe cases of depression. In those with atypical depression, appetite is often signficantly increased and may appear similar to the increase in appetite commonly associated with bvFTD. Severe cases of depression may present as emotional disengagement and social withdrawal which can be mistaken for lack of empathy associated with bvFTD. [5, 76–79]. Despite the overlapping symptomatology between bvFTD and MDD, clinicians generally consider MDD much more prevalent than bvFTD [80, 81]. Clinician's familiarity with similarities and differences between bvFTD and MDD, as well as a thorough evaluation, can improve diagnostic accuracy and help to avoid a delay in care.

Bipolar disorder is a psychiatric disorder characterized by intermittent episodes of mania and depression. The diagnostic criteria for BPD are defined in DSM-5 as a distinct period of abnormally and persistently elevated or irritable mood in addition to seven characteristic features: (1) inflated self-esteem or grandiosity, (2) decreased need for sleep, (3) more talkative than usual or pressure to keep talking, (4) flight of ideas or racing thoughts, (5) distractibility, (6) increased goal-directed activity or psychomotor agitation, and (7) excessive involvement in activities that have a high potential for negative consequences. As in MDD, the symptoms of BPD have a large overlap with those of bvFTD. One of the most salient features in both BPD and bvFTD is excessive impulsivity, however, in BPD it is predominantly associated with manic episodes, though this is not the case in bvFTD. Psychomotor agitation (i.e., engaging in purposeless movements) is another common feature of BPD that may be mistaken for repetitive movements which may be seen in bvFTD [5, 76–79].

Neuroimaging Correlates Between bvFTD and Psychiatric Disorders

Neuroimaging plays an important role in helping to distinguish bvFTD from a primary psychiatric disorder, but it has also been instrumental in helping to establish the underlying neuroanatomical correlates of psychiatric symptoms. In those with MDD and BPD, evidence suggests that structural changes in the brain impact regions involved in bvFTD [6, 82]. Two large meta-analyses examined gray matter abnormalities in MDD and BPD via VBM [82, 83]. Redlich et al.

found that in subjects with MDD, there was a reduction in gray matter volume of the vmPFC, dorsomedial PFC (dmPFC), hippocampus, caudate, and precuneus. In subjects with BPD, there was a reduction in the dlPFC, insula, bilateral hippocampi, amygdala, caudate, thalamus, and putamen [84]. Lu et al. found that in subjects with MDD, there was a reduction of gray matter volume in the vmPFC, ACC, anterior superior temporal gyrus, left caudate, and left hippocampus when compared to healthy controls. In subjects with BPD, there was a reduction in the bilateral insula, superior temporal gyrus, mPFC, ACC, bilateral medial frontal gyrus, and the right medial and inferior temporal gyrus [83].

Regions of volume loss described in these meta-analyses have overlapped with regions involved with bvFTD, described elsewhere in this chapter. The overlapping brain regions of bvFTD, MDD, and BPD may explain the commonality between specific features of these conditions.

Conclusions

Behavioral variant FTD often presents predominately as a neuropsychiatric syndrome early in the disease course. The symptomology of bvFTD and underlying neuroanatomical correlates have overlap with those of primary psychiatric conditions. The commonalities between bvFTD in the early stages, and primary psychiatric conditions, may lead to a misdiagnosis of bvFTD. Clinicians should be aware of this pitfall and be diligent in the evaluation of patients who present with complaints that appear to be psychiatric in nature, especially those who present in late life.

Cases 1

Ms. BH is a right-handed woman with 16 years of education who was employed by the United States government. At baseline, BH was very involved with family and friends and enjoyed volunteering for local community organizations. In her mid-50s, BH began consuming an excessive amount of alcohol at a far greater extent than she had previously. Around this time, she began performing simple repetitive movements which manifested as constantly rubbing her hands together. More complex compulsive behaviors were also noted as she began collecting discarded aluminum cans and other items from the roadside. BH's hygiene progressive worsened and she began showering only once every two weeks.

One year after symptom onset, she was noted by her husband to be increasingly withdrawn socially and not meeting her obligations in the community organizations which she was involved. She became less interested in socializing with family and friends and was less engaged with her husband. On one notable occasion, after the death of a close friend, she did not reach out to her friend's family or attend the funeral. BH stopped completing household chores and began spending most of her day on the sofa watching television. Additionally, she began exhibiting some degree of disinhibition as she began engaging strangers in conversation and disclosing personal details.

Neurological exam revealed difficulty with the Luria sequence, mild postural tremor, and global, symmetric hyperreflexia without clonus.

Neuropsychological testing revealed impairment in verbal and visual memory, visuospatial ability, confrontation naming, working memory, set switching, and response inhibition.

Laboratory studies and electroencephalogram were unremarkable.

FDG-PET was notable for decreased glucose metabolism in the right anterior temporal lobe. Florbetapir [^{18}F] PET was negative for amyloid aggregates. Structural MRI of the brain demonstrated disproportionate volume loss in the right frontotemporal region (Figs. 1 and 2).

Given BH's symptoms of disinhibition, apathy, loss of empathy, repetitive/compulsive behavior, hyperorality, and executive dysfunction in addition to atrophy of the frontal and anterior temporal lobes, BH was ultimately diagnosed with bvFTD.

Case 2

Mr. KC is a right-handed man with 16 years of education who was employed as a photographer.

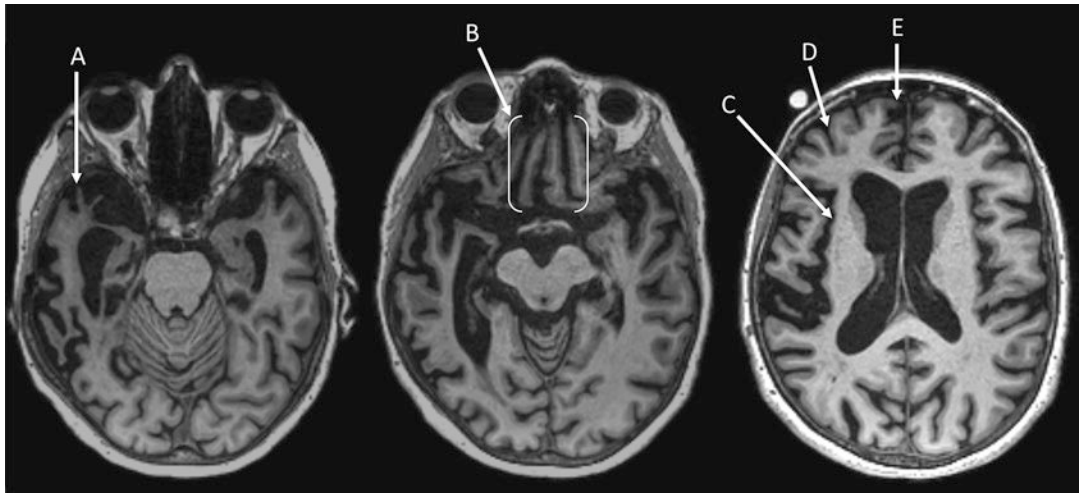

Fig. 1 Axial view in radiological orientation showing asymmetric atrophy of the right anterior temporal lobe (**a**) and the insular cortex (**c**). Other areas of degeneration include the bilateral orbitofrontal cortex with prominence of the orbital fissures bilaterally and the longitudinal cerebral fissure (**b**), the lateral prefrontal cortex (**d**), and the medial prefrontal cortex (**e**)

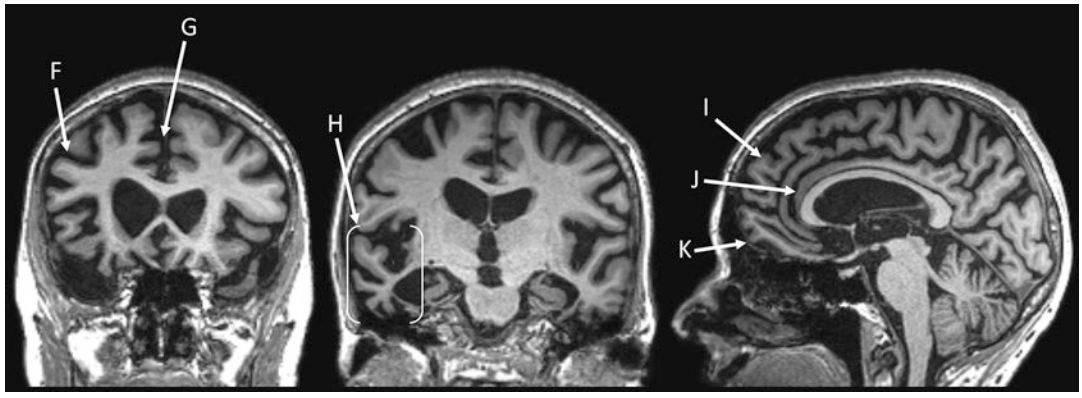

Fig. 2 Coronal view (left and middle) and sagittal view (right) in radiological orientation showing significant areas of atrophy in the lateral prefrontal cortex (**f**), medial prefrontal cortex and anterior cingulate gyrus (**g**), right anterior temporal lobe (**h**), medial prefrontal cortex (**i**), subgenual cingulate gyrus (**j**), and orbitofrontal cortex (**k**)

In his early-50s, KC began experiencing difficulty performing tasks related to his job, and was noted to be repeatedly purchasing incorrect items for his camera. Additionally, the quality of KC's photography began to decline and he became increasingly rigid, often arguing with clients and insisting that his ideas were better.

Approximately 1 year after KC began to experience difficulty at work, he began to experience word-finding difficulty. His speech became increasingly generalized and non-specific, often referring to objects as a "thing" rather than the specific name of the object. Over the following year, KC experienced substantial progressive of word-finding difficulty. He began taking pictures of objects that he was unable to name and used the pictures to communicate. For example, he took pictures of multiple types of fruit and would send the pictures to his wife via text message in order to let her know that they needed more fruit from the store. Further progression of symptoms led to KC being unable to recall the meaning of words

or conceptual knowledge making it difficult to use objects. For example, he was unable to identify what broccoli was or what to do with it. He also had been found performing activities inappropriately on mulitple occasions, such as washing his hands in the toilet rathger than the sink. In addition to language deficits, KC also exhibited memory impairment, visuospatial impairment, and behavioral changes, which included apathy and disinhibition. Notably, his cognition was impaired to the degree that he was unable to work and his wife had to help with most chores.

On neurological examination, KC did not engage in conversation unless directly questioned. He demonstrated echolalia and laughed inappropriately. He was perseverative and stimulus-bound, demonstrating utilization behaviors throughout the evaluation. His thought process was tangential, and he rarely answered questions directly. He could not describe his mood, however, his affect was borderline euphoric. He did not demonstrate appropriate concern or emotion given the nature of some of the topics of discussion. His speech was fluent and grammatically intact but generalized and vague. He was unable to name any items on a task of confrontational naming but was able to correctly describe the function of some of the words. He made semantic paraphasic errors. He was unable to read short, simple sentences. He was unable to write words or draw an animal when asked.

Neuropsychological testing revealed profound impairment in language, most notably impaired confrontation naming, impaired single-word comprehensionm impaired object knowledge. He was also noted to have impaired verbal and visual memory and executive functioning. Structural MRI demonstrated profound asymmetric left temporal atrophy (Fig. 3).

KC was ultimately diagnosed with semantic variant primary progressive aphasia (svPPA) based on the presence of impaired confrontation naming, impaired single word comprehension, impaired object knowledge, alexia, and agraphia. Additionally, MRI demonstrated left anterior temporal lobe atrophy consistent with svPPA.

Case 3

Ms. KA is a right-handed woman with 14 years of education who worked as an accountant. In her early-50s, KA began experiencing slowed speech and was noted to be omitting prepositions and conjunctions when communicating with her children via text message, though there were no spelling errors. The following year, KA began to have difficulty with grammar and using appropriate sentence structure predominantly when writing, resulting in shorter, more simple sentences. KA also began experiencing word-finding difficulty which impacted her ability to communicate.

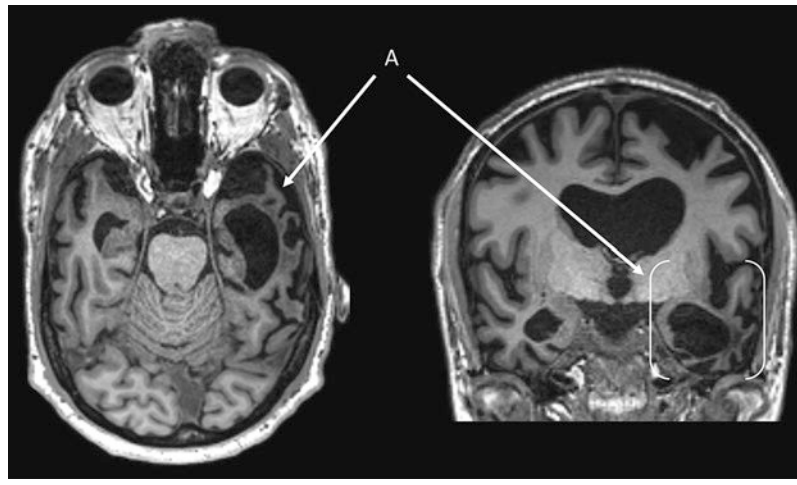

Fig. 3 Axial (left) and sagittal (right) views in radiological orientation showing profound asymmetric left temporal lobe atrophy (**a**)

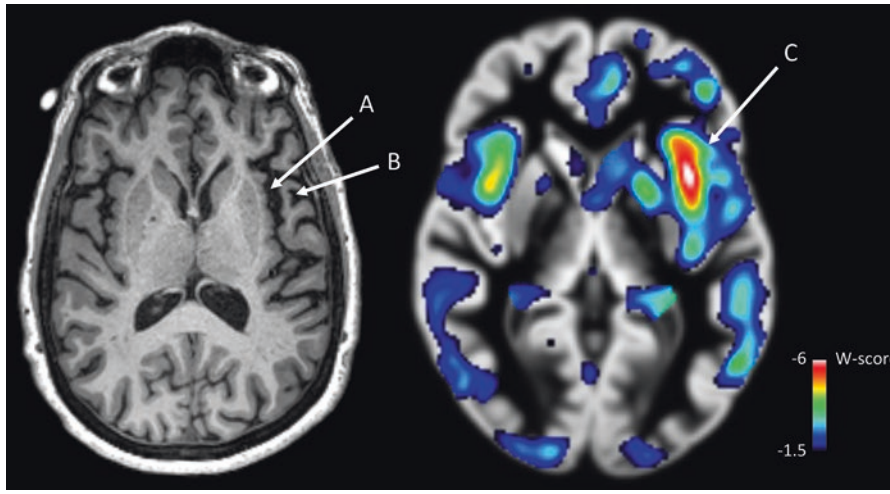

Fig. 4 Axial structural MRI (left) view in radiological orientation showing asymmetric left insular cortex (**a**) and left operculum (**b**) atrophy. Voxel-based morphometry* (VBM) (right) showing the greatest degree of atrophy in the left insular/opercular region (**c**). *Map of this patient's brain volume compared to 534 healthy older controls (age range 44–99 y.o., M ± SD: 68.7 ± 9.1; 220 male/302 female) from the UCSF MAC Hillblom Cohort, adjusted for age, sex, total intracranial volume, and magnet strength. W-scores are interpreted like z-scores, with mean = 0/standard deviation = 1. Negative W-scores represent below-average volume. <−1.50 are below 7th %ile compared to healthy controls and might be considered clinically abnormal. VBM analyses were performed using the open-source Brainsight system, developed at the University of California, San Francisco, Memory and Aging Center by Katherine P. Rankin, Cosmo Mielke, and Paul Sukhanov, and powered by the VLSM script written by Stephen M. Wilson, with funding from the Rainwater Charitable Foundation and the UCSF Chancellor's Fund for Precision Medicine

Three years after the onset of symptoms, she began exhibiting halting, effortful speech. Reading and verbal comprehension was impaired, particularly to long, syntactically complex sentences. Writing was much more difficult than speaking, though she was still able to compose letters and emails with the help of her family. Despite her language impairment, she remained fully independent and continued to work as an accountant without additional difficulty.

On neurological examination, KA was exhibited halting, effortful speech, with agrammatism and frequent phonological errors. When she spoke, her sentences were short and grammatically simplistic. Comprehension of syntactically complex sentences was impaired. Single-word comprehension and object knowledge were spared. She exhibits subtle nondominant limb apraxia and orobuccal apraxia.

On neuropsychological testing, she demonstrated severely impaired sentence repetition, diminished verbal agility, and agrammatism with relatively preserved naming, comprehension, and semantic knowledge. Additionally, she exhibited impaired lexical fluency, markedly impaired design fluency, executive dysfunction, and mild visual memory deficits.

Ms. KA was ultimately diagnosed with nonfluent variant primary progressive aphasia (nfvPPA) on the basis of her effortful, halting speech with agrammatism, spared single-word comprehension and object knowledge, and neuroimaging demonstrating predominant left fronto-insular atrophy (Fig. 4).

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Nosology of Primary Progressive Aphasia and the Neuropathology of Language

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Introduction

Primary progressive aphasia (PPA) is a major syndrome of frontotemporal lobar degeneration (FTLD) and accounts for nearly 25% of all FTLD cases [1]. Approximately 60% of PPA is associated with FTLD and the remaining 40% with the neuropathology of Alzheimer's disease (AD). Information on PPA prevalence is limited. One study from the UK suggests an approximate prevalence of 3–4/100,000, a level comparable to what has been reported for ALS [1]. The one common denominator for all PPA, whether caused by FTLD or AD, is the preferential degeneration of the language network, usually located in the left hemisphere of the brain. Current research on primary progressive aphasia is evolving in multiple directions. For one, the variety of the aphasic disturbances continues to fuel discussion on nomenclature and clinical classification. Second, the selective dissolution of individual language domains is offering new paradigms for exploring the functional anatomy of language, a pursuit that has already prompted modifications of classic models. Third, the multiplicity of the underlying degenerative diseases is generating new insights on the heterogeneity of dementias, the probabilistic relationship of syndrome to

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pathology, and the mechanisms of selective vulnerability. Fourth, there is lively interest in formulating personalized interventions aimed not only at the nature of the language disturbance but also at the biology of the underlying disease entity. These are some of the current trends that will be reviewed in this chapter. Given the constraints of space and the vast literature on PPA, the account will be selective and based predominantly on the PPA research programs at Northwestern University where a cohort of 235 PPA patients have been enrolled, 97 of whom have come to brain autopsy.

Diagnosis, Nomenclature, and Subtyping

The existence of progressive language disorders had been known for more than 100 years. Pick, Sérieux, Dejerine, Franceschi, and Rosenfeld were among the first to report such patients during the late nineteenth and early twentieth centuries [2–7]. However, this topic did not attract much, if any, attention during most of the twentieth century. The current resurgence of interest in this condition can be traced to the 1982 report of six patients who experienced a slowly progressive aphasia without other cognitive or behavioral impairments [8]. The syndrome was named "primary progressive aphasia," and diagnostic criteria were formulated [9, 10]. The following decades witnessed a rapidly expanding literature on PPA and on overlapping entities designated progressive nonfluent aphasia (PNFA) and semantic dementia (SD) [11]. For a number of years, research on PNFA and SD developed in parallel to research on PPA. In 2011, an international group of investigators presented classification guidelines that incorporated PNFA and SD under the PPA umbrella [12]. This unitary approach stimulated rapid progress in this field.

Three features define PPA: (1) adult-onset and progressive impairment of language (not just speech), (2) absence of other consequential behavioral or cognitive deficits for approximately the first 2 years, and (3) neurodegenerative disease as the only cause of impairment [10]. These criteria help to filter out patients where progressive aphasias arise in conjunction with equally prominent speech apraxia, behavioral disturbances, loss of memory for recent events, associative agnosias, or visuospatial deficits. In the course of diagnostic evaluation, patients may show subtle impairments in non-language tasks, especially those related to memory and executive function. Such abnormalities of test performance do not by themselves preclude a PPA diagnosis unless they are associated with limitations of daily life in the corresponding non-language domains.

Many neuropsychological tests require verbal responses and verbal instructions. The clinician needs to consider the influence of the aphasia on these aspects of performance. For example, a patient with PPA who cannot name a famous face is not necessarily prosopagnosic, a patient who cannot verbalize the nature of an object does not necessarily lack knowledge of the object, and a patient who cannot learn a word list is not necessarily amnestic. Conversely, patients who cannot produce words because of articulation deficits, those who cannot repeat language because of general working memory limitations, those who misname objects or faces they do not recognize, or those who have impoverished speech because of abulia or impaired executive function are not necessarily aphasic. As in the case of many other syndromes, the diagnosis of PPA relies on the judgment and experience of the clinician. While clear-cut cases do exist, there are also cases where the salience and primacy of the aphasia will generate debate, especially if the patient is examined a few years after symptom onset. In some patients, the aphasia will remain the only salient feature for over a decade [13]. Other patients, however, may first come to a specialty clinic at a time when the disease has progressed to encompass other cognitive domains. The term "PPA plus" (PPA+) can be used to designate such patients, based on the assumption that the disease had started as PPA, but that it had since spread beyond the language network [14].

In contrast to many other dementias, where the patient has little insight into the predicament, patients with PPA are usually the first to notice

and report the difficulty. At those stages of the disease, MRI and metabolic positron emission tomography (PET) scans may be negative. The absence of positive neurodiagnostic tests, combined with lack of recognition of these symptoms in general practice, may lead to unwarranted referrals to otolaryngologists or psychiatrists [15]. Patients and families often ask whether the diagnosis is PPA or AD. When AD biomarkers (such as amyloid and phospho-tau in cerebrospinal fluid [CSF] or amyloid PET scans) are positive, the clinician will have to explain that the patient has both PPA and AD, that PPA refers to the symptoms that bring the patient to the clinic, and that AD refers to the abnormal amyloid and tau proteins in the brain that attack the language centers. There was a time when PPA was underdiagnosed. There are now instances where it seems to be overdiagnosed, probably because language impairments can be so prominent during the office evaluation that other equally substantial cognitive and behavioral impairments become overlooked. This issue comes up most commonly in patients with prominent apraxia of speech or executive dysfunction who are also aphasic. We give these patient descriptive diagnoses such as "apraxia of speech with aphasia" or "aphasic frontal syndrome."

Language impairment can encompass word retrieval, object naming, sentence construction, or language comprehension, either singly or in combination. Once the PPA diagnosis is established, the subtyping exercise can be initiated. At the time of writing, the 2011 guidelines dominate this process [12]. They help to classify PPA into nonfluent/agrammatic, logopenic, and semantic variants. Although this system has been immensely influential and is even frequently mandated during the review of manuscripts submitted for publication, it has widely recognized shortcomings [16–18]. For one, a strict adherence to the 2011 guidelines entails arduous assessment of nearly a dozen separate aspects of language. Second, even if the guidelines are strictly applied, approximately one-third of the patients will fail to be classified into any of the three variants. Third, there are certain feature clusters that allow the same patient to simultaneously fit the designation of both nonfluent/agrammatic and logopenic PPA. Yet another challenge is posed by the evolution over time, so that a patient who fits the logopenic subtype initially may fit criteria for one of the other two subtypes as the disease progresses.

The following modifications have helped us address some of these concerns [16]. (1) The relative preservation of both grammar and comprehension is made to be a core feature of the logopenic variant. This prevents the double assignment problem. (2) In contrast to the 2011 guidelines, repetition impairment is not considered an obligatory core feature of the logopenic variant. This practice reduces the number of unclassifiable patients. (3) Patients with combined impairments of grammar and word comprehension even early in the disease, and who would therefore remain unclassifiable by the 2011 guidelines, make up a fourth variant of "mixed" PPA. (4) The semantic variant is diagnosed when poor word comprehension is the principal feature. When additional and equally prominent impairments of object or face recognition (not just naming) are detected, a diagnosis of semantic dementia (SD) is made [11]. This recommendation is at odds with the 2011 guidelines, which would diagnose semantic PPA even in patients with significant face and object recognition impairment (i.e., visual associative agnosia). The justification for the distinction of PPA from SD is summarized in the section on the anatomy of language.

The modifications listed above lead to a classification method based on a template where the Y-axis represents worsening impairment in the grammaticality of sentence construction and the X-axis represents worsening impairment in single word comprehension [15]. Each of the four PPA subtypes will cluster within a different quadrant of this template. The *nonfluent/agrammatic* PPA patients, for example, will cluster in the upper left quadrant (impaired grammar but spared comprehension); the *semantic* PPA patients will cluster in the lower right quadrant (impaired comprehension but spared grammar); the *mixed* PPA patients will cluster in the lower left quadrant (combined impairments of grammar

and comprehension); and the *logopenic* PPA patients will cluster in the upper right quadrant (relatively spared grammar and comprehension). The logopenic group would have met the PPA criteria through impairments of word retrieval, naming, and spelling. Specific tests for assessing grammaticality of sentence construction and word comprehension and their normative values have been reported [15]. As patterns of agrammatism vary greatly from language to language, considerable attention is being directed to the adaptation of grammar tests for languages other than English [19].

Some logopenic patients maintain fluency as they circumvent word finding failures through circumlocution; others pause after word retrieval failures and produce halting nonfluent speech that appears similar to what is seen in patients with nonfluent/agrammatic PPA. Word finding impairments and paraphasias may make it impossible to gauge a sentence grammaticality. The delineation of logopenic from agrammatic PPA can thus be quite challenging [17]. Quantitative analyses of speech samples show that the nonfluent/agrammatic patients make word finding pauses that are longer before verbs, whereas logopenic patients make pauses that are longer before nouns [20]. Furthermore, patients with nonfluent/agrammatic PPA display a preferential impairment of verb rather than object naming, whereas the converse may be seen in logopenic PPA [21]. When research objectives necessitate such distinctions, these features may help to establish a quantitative differentiation of nonfluent/agrammatic from logopenic forms of PPA. Subtyping need not become an end onto itself. For purposes of both research and treatment, the emphasis could also be on single parameters, such as grammar or naming, across all subjects and regardless of subtype.

The 2011 guidelines did not prescribe acronyms for the three variants. At present, *non-fluent variant* (nfvPPA), *logopenic variant* (lvPPA), and *semantic variant* (svPPA) are the most popular choices. Alternative acronyms such as naPPA, agPPA, PPA-NFV, LPA, and PPA-SV have also been used, albeit more rarely [22–25]. The "nfv" prefix is particularly problematic because it appears to overlook grammar, which is the single most characteristic impairment of this subtype. The choice of "nfv" was probably based on experience derived from stroke aphasia where low fluency can be used as a proxy for agrammatism. In PPA, grammar and fluency can be dissociated, especially in logopenic patients where long word finding pauses diminish fluency but without grammatical impairment [26]. Based on these considerations and also in order to underscore the primacy of the PPA diagnosis, we have used the alternative acronyms of PPA-G, PPA-L, PPA-S and PPA-M for the nonfluent/agrammatic, logopenic, semantic and mixed variants, respectively. It may take another collective international effort to determine whether the 2011 consensus guidelines should be modified along the lines listed above and whether the acronyms can be harmonized.

Clinical progression patterns vary by subtype and are likely to reflect the differential anatomical trajectories of disease spread. In PPA-S, the spread of atrophy from the anterior temporal lobe to orbitofrontal, insular, or contralateral temporal lobe can lead to the additional face and object recognition impairments of SD, and to the behavioral abnormalities seen in behavioral variant frontotemporal dementia (bvFTD). In PPA-G, spread of atrophy from the inferior frontal gyrus (IFG) to other premotor and frontal cortices can lead to the abnormalities seen in apraxia of speech, corticobasal syndrome, supranuclear ophthalmoplegia, and frontal-type executive dysfunction. In PPA-L, spread of atrophy from the temporoparietal junction (TPJ) to surrounding cortices can lead to additional impairments of explicit memory and constructions. For all subtypes, the spread of atrophy tends to be more pronounced in the left hemisphere, and there are substantial interindividual differences in the speed and trajectory of progression [27].

Contributions to the Anatomy of Language

The classic Wernicke-Lichtheim-Geschwind model of language revolved around two epicenters, namely Broca's area in the inferior frontal gyrus (IFG) and Wernicke's area in the temporo-

parietal junction (TPJ), a region that can be said to encompass parts of the inferior parietal lobule and the posterior segments of the superior and middle temporal gyri [28] (Fig. 1). The former has been linked to fluency and grammar and the latter to language comprehension. The literature of the past 150 years displays greater agreement on the location and function of Broca's area than of Wernicke's area [28]. These two epicenters are connected through the arcuate fasciculus, which is thought to play a critical role in language repetition [29]. This basic model has undergone major revisions through investigations with functional imaging, event-related potentials, and sophisticated neuropsychological assessments [30–32].

Each of these approaches has advantages and disadvantages. Cerebrovascular lesions cause sudden and irreversible destruction of the core lesion site. However, the damage usually extends into deep white matter. The exact contribution of the damaged cortical region to the ensuing language impairment is therefore difficult to specify. Functional mapping approaches based on MRI and electrical recordings, on the other hand, can reveal activity confined to the cerebral cortex but cannot differentiate areas that are critical for a function from those that have collateral participatory roles.

Investigations based on focal cortical atrophy can circumvent some of these shortcomings. Regions where the magnitude of cortical thinning correlates with the magnitude of impairment can be said to have critical (rather than participatory) roles in maintaining the integrity of that function. Consequently, PPA has offered new tools for investigating the cortical anatomy of the language network without the deep white matter problem of stroke or the collateral activation dilemma of functional brain mapping. Nonetheless, clinicoanatomical correlations in PPA are not without caveats. For one, the slow evolution of the lesion is likely to trigger compensatory plasticity that may complicate the interpretation of correlations. Second, even areas of peak atrophy may contain residual neurons that could sustain some functionality of that region [33]. Third, each neuropathologic entity may trigger a different pattern of cortical injury. For example, the neurofibrillary tangles of AD have a predilection for deep cortical layers whereas the opposite is the case for Pick's disease.

Despite these potential complications, clinicoanatomical investigations on PPA have generated new insights into the functional anatomy of language. Each PPA variant is associated with a characteristic location of peak atrophy, for instance, Broca's area (IFG) in PPA-G, Wernicke's area (TPJ) in PPA-L, and the anterior half of the temporal lobe (ATL) in PPA-S [34–36]. The anatomical correlate of PPA-G is in keeping with prevailing models of language, which give Broca's area a critical role in the maintenance of fluency and grammar [37]. The relationships in PPA-L and PPA-S, however, are in conflict with classic aphasiology and also with most contemporary models of language. For one, traditional models of language exclude the ATL. For example, an influential review published at the height of twentieth-century aphasiology states that the probability that a lesion would impair comprehension is "very high in or near the first temporal gyrus, and fades out with different gradients (varying among individuals) toward the poles. And by the time it gets to any pole (occipital, temporal, or frontal) the probability is essentially zero" [38]. Research on PPA-S has contradicted this statement by showing that damage to the left ATL, including the temporal pole and anterior fusiform gyrus, causes severe impairments of word comprehension. Based on this finding, a proposal has been made that this region should be considered a core component of the language network [28].

This proposal has generated considerable debate. The disagreement revolves around the alternative characterization of ATL as an amodal hub for all semantic knowledge, verbal and nonverbal. Consequently, ATL damage should cause more than a language impairment (i.e., aphasia) and should give rise to a universal loss of semantic knowledge not only for words but also for faces and objects [39]. Based on this point of view, the syndrome of ATL damage was designated semantic dementia (SD), a syndrome

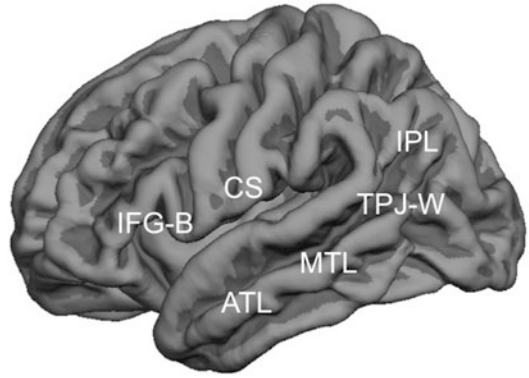

Fig. 1 Major components of the left hemisphere language network – ATL: The acronym ATL will be used to refer to the anterior third of the temporal lobe including the temporal pole; CS (the central sulcus) is shown as a reference point, IFG-B (the inferior frontal gyrus) contains Broca's area, IPL (inferior parietal) lobule, MTL (the middle third of the temporal lobe), TPJ-W (the temporoparietal junction) contains the posterior third of the temporal lobe and the immediately adjacent parts of the inferior parietal lobule. Although the exact site of Wernicke's area remains ambiguous, it is usually considered to be located within the TPJ-W and adjacent parts of the MTL

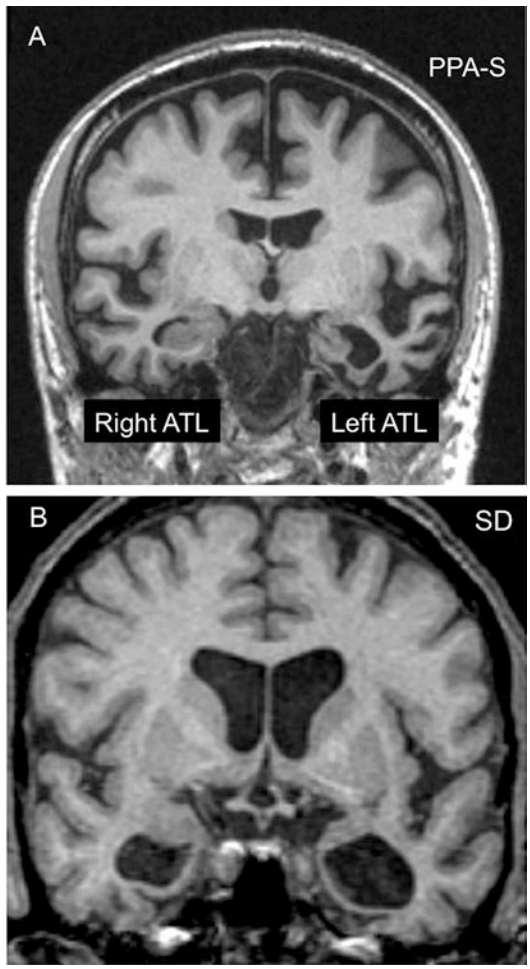

Fig. 2 PPA-S versus SD. Figure 2a shows the MRI scan of a right-handed man with symptom onset at the age of 59. On examination, 7 years later, the clinical pattern was PPA-S and atrophy was much more prominent in the left anterior temporal lobe (ATL). At that time, he had severe word comprehension impairments but no difficulty with non-verbal object recognition either in testing or in everyday life. In comparison, Fig. 2b shows the MRI scan of a right-handed man with symptom onset at the age of 65. Three years later, at his initial visit, ATL atrophy was bilateral. He had prominent word comprehension and object recognition impairments. This combination led to a subsequent diagnosis of semantic dementia (SD)

defined by the combination of semantic aphasia (word comprehension deficit) with visual associative agnosia (loss of face and object recognition) [11, 39]. Such patients would not fit the diagnostic criteria for PPA since the aphasia would no longer constitute the dominant feature.

The disagreement on the nature of the syndrome caused by ATL damage can be resolved by considering the influence of hemispheric specialization [28, 40, 41]. Clinical observations and specially designed experimental tasks show that PPA-S is a selective aphasic syndrome of the left anterior temporal lobe, whereas the SD syndrome reflects a wider deficit with a more bilateral anatomical substrate [42–45]. The patients with left ATL damage may not be able to name objects and faces but are generally cognizant of their identity and nature [46]. It should be pointed out, however, that many PPA-S patients may also have minor atrophy in the right anterior temporal lobe, and that further spread of neurodegeneration within the right hemisphere may lead some, but not all, to eventually develop the additional face and object recognition deficits of SD. It is not surprising, therefore, that some authors have considered PPA-S and SD to be the two sides of the same coin [40, 41]. The question is whether syndromic designations should be based on clinical presentation at disease onset, as we advocate, or based on possible progression trajectories (Fig. 2). When ATL atrophy is predominantly right-sided, the patient may present with one of three syndromes, SD, non-aphasic associative agnosia, or bvFTD [47, 48].

Exactly how the left ATL contributes to word comprehension is a topic of active investigation. Resting state functional imaging experiments show that the left ATL has left-sided asymmetric functional connectivity patterns that support its inclusion within the language network [49]. In our cohort, all right-handed patients with severe word comprehension impairment have also had substantial left ATL atrophy extending all the way into the pole. However, some patients with such a location of atrophy may have severe anomia in the absence of word comprehension impairment. In these patients, the distinctive comprehension impairment of PPA-S emerges as the atrophy extends posteriorly from the anterior tip of the left temporal lobe into adjacent parts of the middle portion of the temporal lobe (MTL), especially the middle temporal gyrus (MTG) [28]. In keeping with this observation, functional MRI studies in PPA and clinicoanatomical correlations in stroke have shown that the connectivity of the mid-to-posterior parts of the MTG with ATL and other parts of the language network may have important roles in sustaining word comprehension [50, 51]. In our experience, isolated atrophy of the middle parts of the temporal lobe in PPA has not been associated with impairment of this function [28]. Damage to the left ATL may therefore be necessary but not always sufficient for word recognition impairment. Posterior expansion of damage into the middle parts of the temporal lobe may also be required.

Patients with PPA-S have severe naming impairments principally because they do not understand the meaning of the word that denotes the object they are asked to name [46]. The impairment initially undermines the comprehension of a word at its specific level of meaning (does the word denote a strawberry or a cherry) but later generalizes to the generic meaning of the word (does the word denote a fruit or an animal) [52]. Based on these observations in PPA-S, the left ATL can be conceptualized as a transmodal region of cortex where sensory word form information is linked to the multimodal associations that collectively encode the meaning of the word [28, 53]. Word recognition at a specific level of meaning requires more extensive associative elaboration and would therefore be more vulnerable to early stages of neurodegeneration.

Another unexpected outcome of research on PPA was the finding that patients with the logopenic variant have normal single word comprehension despite peak atrophy sites that encompass Wernicke's area as defined above. In fact, regression analyses in 73 PPA patients showed no correlation between atrophy in Wernicke's area and impairment of word comprehension [28, 54]. In addition to clinicoanatomical correlations in PPA-L, which have shown that severe cortical degeneration of Wernicke's area does not impair single word comprehension, investiga-

tions on PPA-S have shown that an intact Wernicke's area is not sufficient to sustain word comprehension if the ATL is damaged. The body of work on PPA therefore leads to the conclusion that the cortex of Wernicke's area is neither necessary nor sufficient for word comprehension. This conclusion can be reconciled with classic aphasiology by keeping in mind that nearly all reports linking Wernicke's area to word comprehension are based on cerebrovascular lesions. Such lesions include not only the cortex of Wernicke's area but also deep white matter axons, such as those in the middle longitudinal fasciculus [55], that are likely to carry projections of otherwise intact distal posterior and contralateral cortices. The resultant additional cortical disconnections may explain why stroke in Wernicke's *region* impairs word comprehension while neurodegeneration in Wernicke's *cortex* does not [54].

The large-scale network model posits that each network node mediates critical (or essential) as well as ancillary (or sustaining) functions related to its principal cognitive domain [56, 57]. While damage to a given node may not cause fixed impairments of its ancillary functionalities, the overall computational flexibility of the network for mediating that task may be compromised. These principles apply to the role of Wernicke's area in language comprehension. For example, agrammatic and logopenic PPA patients whose atrophy encompasses Wernicke's area but not the ATL, and who have normal word comprehension in standard tests and daily life, display abnormally prolonged semantic interference effects and loss of the N400 semantic incongruence potential [52, 58]. Furthermore, functional magnetic resonance imaging (fMRI) investigations using synonym identification tasks revealed activations not only in the anterior temporal lobe but also in regions overlapping Wernicke's area [59, 60]. The cerebral cortex within Wernicke's area therefore serves an ancillary role in word comprehension. Multiple lines of evidence show that Wernicke's area plays a critical role in language repetition, a finding that is in keeping with observations in stroke aphasia [54]. This area is important for language repetition presumably because it links phonologic word form codes to their articulatory sequences [61–63].

An additional contribution of PPA to the anatomy of language comes through the discovery of the aslant tract, a pathway that connects the core language network with dorsal premotor cortex and appears to play a major role in sustaining fluency [64]. Patients with PPA may also show patterns of aphasia that have not been observed in other settings. For example, some patients may show a preferential inability to name objects orally but not in writing and fail to understand words they hear but not those they read [65]. These patients do not fit the pattern seen in pure word deafness because they are anomic and they do not fit the pattern of auditory agnosia because they can match objects to their characteristic sounds. Investigations on this small group of patients have helped to explore the functionality of a putative "auditory word form area" that sits at the confluence of modality-specific pathways for word comprehension and language repetition.

The totality of these investigations on PPA depicts a large-scale language network built upon the interactive functionalities of dorsal and ventral (rather than anterior and posterior) streams of processing [31]. The dorsal route mediates phonological encoding, repetition, articulatory programming, fluency, word retrieval and also the sequencing of morphemes and words into grammatically correct sentences. The ventral route mediates the lexicosemantic processes of object naming and word comprehension. Word finding in speech is a joint function of both routes and therefore the most common presenting complaint in PPA.

Asymmetry of Neuropathology and Genetics

In our group of 97 consecutive autopsies, the primary neuropathology was FTLD with tauopathy (FTLD-tau) in 29%, FTLD with transactive response DNA-binding protein 43 (FTLD-TDP) in 25%, and AD in 44%. All three major neuropathologic forms of FTLD-tau (Pick's disease,

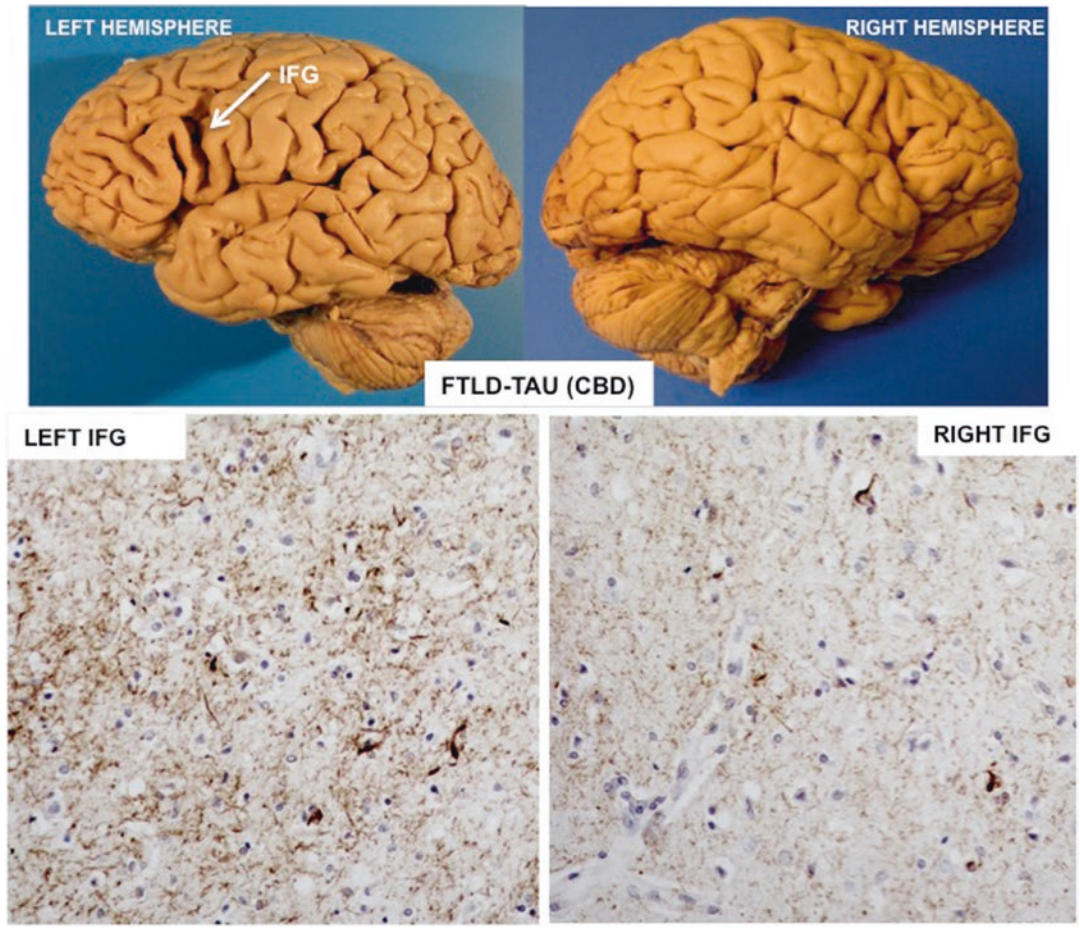

Fig. 3 Asymmetry of neurodegeneration. Postmortem examination of a right-handed woman with symptom onset at the age of 72 and findings of agrammatic PPA with prominent word finding impairments. Death occurred 6 years later. The primary neuropathology was found to be FTLD-tau of the CBD type. The top figures show the profound asymmetry of atrophy. There is an almost cystic area of atrophy around the left inferior frontal gyrus (IFG) but no comparable atrophy of the right. The photomicrographs at the bottom, based on phosphotau immunostaining in the same patient, show the tauopathy to be more intense in the left IFG than in the right

corticobasal degeneration [CBD], progressive supranuclear palsy [PSP]), and all three major forms of FTLD-TDP (types A, B and C) were represented. There were some disease-specific preferential patterns of atrophy. For example, AD almost always led to peak atrophy that included the temporoparietal junction; TDP-C almost always led to severe anterior temporal atrophy; Pick's disease routinely caused combined atrophy of anterior temporal and prefrontal cortex; and PSP and CBD tended to be associated with surprisingly modest cortical atrophy, usually in dorsal premotor or inferior frontal cortex. The one common denominator of nearly all cases is the leftward asymmetry of the atrophy (Figs. 3 and 4). What is surprising is that the asymmetry is almost always maintained up to the time of death. The initial predilection of the language-dominant left hemisphere is therefore not a random event at disease onset but a core biological feature of the syndrome.

There was nearly equal representation of males and females in our autopsy cohort. Age of onset varied from 41 to 80 with a mean of 61 ± 8 years. Survival from symptom onset to death varied from 2 to 23 years with a mean of

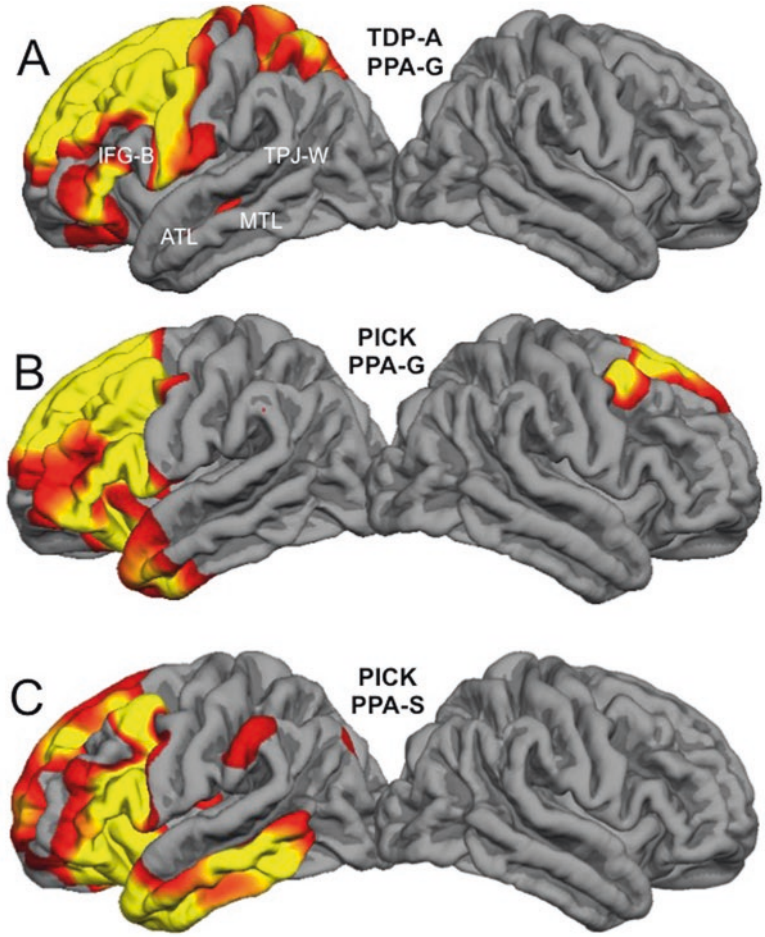

Fig. 4 Correspondences of pathology, atrophy, and syndrome. Quantitative MRI morphometry in three right-handed patients who had come to postmortem brain autopsy. Areas of significant cortical thinning compared to controls are shown in red and yellow. (**a**) Onset of PPA-G was at the age of 65. The scan was obtained 2 years after onset. At postmortem, the primary pathology was FTLD-TDP type A. (**b**) Onset of PP-G was at the age of 57. The scan was obtained 5 years after onset. At postmortem, the primary pathology was Pick's disease. (**c**) Onset of PPA-S was at the age of 62. The scan was obtained 5 years after onset. At postmortem, the primary pathology was Pick's disease. Despite the differences in neuropathology and clinical syndrome, the one common denominator is the profound leftward asymmetry of atrophy. Abbreviations: ATL anterior third of the temporal lobe, IFG-B inferior frontal gyrus where Broca's area is located, MTL middle third of the temporal lobe, TPJ-W temporoparietal junction where Wernicke's area is located

9.69 ± 3.93. Survival tended to be the longest for those with AD (10.8 ± 4.4) and FTLD-TDP type C (12.4 ± 2.6) and shortest for those with FTLD-TDP types A and B (5.8 ± 2.2). In keeping with these different rates of progression, FTLD-TDP aggregates extracted from subjects with type A pathology were shown to be more cytotoxic than aggregates from subjects with type C pathology [66].

The relationship of PPA variants to the underlying neuropathologic entity is probabilistic rather than absolute [67]. Autopsy data show that the vast majority of PPA-S cases have had TDP-C pathology but approximately 20% have had Pick's disease; the majority of PPA-G cases have had FTLD-tau (all types) but approximately 30% have had FTLD-TDP or AD; the majority of PPA-L cases have had AD but 30% have shown

FTLD-tau or FTLD-TDP. Figure 4 illustrates the clinicopathologic heterogeneity of PPA, namely that the same neuropathologic entity can cause more than one aphasic variant and that the same PPA variant may be caused by more than one neuropathologic entity. As shown in Fig. 4a and b, FTLD-TDP type A and Pick's disease cause nearly identical peak atrophy patterns that extend into the frontal components of the language network known to underlie grammar and fluency, giving rise to the concordant syndrome of PPA-G. Figure 4b and c raise challenging questions. They show atrophy patterns in two different patients with Pick's disease at autopsy, one with PPA-G (Fig. 4b), the other with PPA-S (Fig. 4c). As explained in the section on the anatomy of language, the semantic aphasia associated with Fig. 4c could be attributed to the posterior expansion of atrophy from ATL into more middle sections of the temporal lobe. However, it is difficult to understand why the patient in Fig. 4c was not also agrammatic since the frontal atrophy is nearly as extensive as in the other two cases with PPA-G. Perhaps this discrepancy can be blamed on vagaries of cortical morphometry performed on single subjects or, alternatively, on individual variations in the functional anatomy of the language network.

During life, cortical thinning (i.e., atrophy) and hypometabolism are the two most conspicuous markers of asymmetric neurodegeneration. Considerable progress has been made in exploring the potential cellular substrates of the asymmetrical atrophy (Fig. 3). For example, neurofibrillary tangles (NFT) (but not the amyloid plaques) of AD, tauopathy of CBD/PSP, Pick bodies, abnormal TDP-43 deposits of FTLD-TDP, activated microglia, and the extent of neuronal atrophy/loss tend to be more prominent in the left hemisphere than in the right hemisphere and also more prominent in language-related than other cortical areas of the left hemisphere [68–73]. In one left-handed PPA patient with documented right hemisphere language dominance and FTLD-TDP neuropathology, cortical atrophy and neurodegeneration markers were more prominent in the right hemisphere [74]. In at least some PPA patients with AD neuropathology, NFT may be more numerous in the language-related cortices of the left hemisphere than in the medial temporal areas, a distribution that deviates from the Braak and Braak pattern of neuropathology and underlies the atypical preservation of episodic memory in these patients [71, 73].

Quantitative investigations have also looked into the concordance of PPA subtypes with regional variations of neurodegeneration markers. A study of four right-handed PPA patients with FTLD-TDP type A neuropathology showed that the two patients with PPA-G displayed the highest density of TDP-43 precipitates in the frontal components of the language network, whereas the two with PPA-L displayed the highest density of precipitates in the temporoparietal components of the language network [69]. The cellular pathology in PPA can therefore asymmetrically target parts of the language-dominant hemisphere in a way that also mirrors the anatomical predilection patterns of the specific PPA variant. In the future, it would be useful to conduct similar analyses based on synaptic density. Some patients, especially those with PPA-G and FTLD-tau, may have no detectable cortical atrophy in the initial years of disease. These patients display abnormalities of functional connectivity, suggesting that physiological perturbations of the language network may precede atrophy [75]. In this group of patients, the neurodegeneration may be particularly prominent in subcortical white matter [76]. It is important to keep in mind that the identity of the disease marker that shows the best correlation with clinical dysfunction can change over time. Inclusions are likely to reflect leading indicators and would be expected to show the best correlation with clinical patterns in early disease stages, whereas neuronal death is likely to represent a trailing indicator more closely aligned with clinical patterns late in the disease.

In our autopsy cohort of 97 cases, a third of TDP-A cases had granulin (*GRN*) mutations. No other disease-causing mutations were encountered. Other studies have also shown that mutations in the *GRN* gene constitute the most common genetic correlate of familial PPA [77]. In such *GRN* families, some members may have PPA and others bvFTD [78, 79]. Rarely, all

affected members of a *GRN* family will have PPA [80]. Even then, the type of aphasia may differ from one sibling to another and there is considerable heterogeneity of PPA subtypes associated with *GRN* mutations [81, 82]. The literature also contains rare associations of PPA with mutations in the presenilin (*PSEN1*), tau (*MAPT*), and *C9orf72* genes [83–85]. The most common clinical variants associated with dominantly inherited diseases are PPA-G and PPA-L, but rare cases of PPA-S have been reported [82]. The cellular neuropathology is FTLD-TDP type A in *GRN* mutations, FTLD-TDP type B in *C9orf72* mutations, and any one of the major FTLD-tau types in *MAPT* mutations. FTLD-TDP type C is very rarely, if ever, associated with known disease-causing mutations [86–88].

The heterogeneity of phenotypes encountered within *GRN* families shows that molecular underpinnings alone are not sufficient to account for the patterns of selective vulnerability and their clinical manifestation. The biological mechanisms underlying the selective and asymmetric involvement of the language-dominant hemisphere in PPA remain to be elucidated. One line of investigation has focused on the significantly higher frequency of learning disabilities, including dyslexia, in PPA patients and their first-degree relatives compared to control populations and patients with other dementias [89–91]. Follow-up research has replicated this association and raised the possibility that it may be peculiar to PPA-L [92]. Some families of PPA probands have strikingly high prevalence of developmental dyslexia in siblings or children [89]. We saw one family where seven of nine siblings of a PPA patient had findings indicative of developmental dyslexia [93]. As a group, the dyslexic siblings in this family had decreased functional connectivity within the language network although none had any findings of PPA. These observations led to the speculation that at least some cases of PPA could be arising on a developmentally or genetically based vulnerability of the left hemisphere language network. In some family members, this vulnerability would interfere with the acquisition of language and lead to dyslexia, while in others, it would make the language network a locus of least resistance for the effects of an independently arising neurodegenerative process, leading to PPA [33]. So far, linkage studies addressing this hypothesis have not detected an association between PPA and known dyslexia genes [77]. Given the polygenic nature of dyslexia, negative results may reflect an insufficient number of cases.

Therapeutic Interventions

The heterogeneity of PPA highlights the need to individualize therapeutic approaches. Interventions in individual patients should target the underlying disease as well as the symptom complex. The former step requires the use of in vivo biomarkers. There are excellent CSF and PET biomarkers for detecting PPA patients with AD neuropathology and blood-based biomarkers may be on the horizon. However, current tau ligands for PET do not yet offer reliable identification of non-AD tauopathies associated with CBD, PSP, and Pick's disease [94]. When such biomarkers become available, they will enable the identification of PPA patients with FTLD-tau and, by exclusion, those with FTLD-TDP. The goal of these diagnostic investigations is to prescribe approved medications (e.g., cholinesterase inhibitors if AD) and to channel the patient to relevant disease-specific clinical trials. Although clinical examination is rarely sufficient to specify the underlying disease entity, we have found that prominent single word comprehension deficits that arise as the most salient feature of PPA are never associated with AD. The presence of this feature may therefore be used to forego AD biomarker testing.

The nonpharmacologic interventions aimed at the language impairment include speech therapy and brain stimulation modalities such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) [95]. Promising effects have been reported following left hemisphere tDTS in PPA-S [96]. If confirmed, this may well be the first time that brain stimulation will be shown to have therapeutic effects in an FTLD syndrome. Evidence for the effectiveness

of speech-language therapy in PPA is emerging [97–99]. Utilization of this intervention modality is low in part due to the misconception that speech-language therapy is not appropriate for neurodegenerative syndromes where worsening is inevitable [100, 101]. An additional barrier is the lack of familiarity of speech-language pathologists with neurodegenerative conditions. Speech-language therapy in PPA requires personalization to fit the pattern of impairment and its evolution over time. For example, there are patients with modality-selective impairments of naming and word comprehension who could benefit from treatments emphasizing the relatively spared channels of language processing [65]. Additional questions to be resolved in the course of speech-language therapy include the relative usefulness of multicomponent, impairment-based, or compensatory approaches and the comparative benefits of group, dyadic, or patient-only approaches [102]. In each case, ecologically meaningful and statistically robust outcome measures will need to be devised.

Recent developments in telemedicine raise the possibility of delivering speech-language therapy in the home of the individual living with PPA [103, 104]. Communication Bridge, for example, is a two-arm, randomized control trial of speech-language intervention delivered through video chat for individuals with PPA [104]. The experimental arm uses a client-informed, dyadic approach for individuals with PPA and their communication partner. Impairment-based exercises using personalized stimuli and compensatory strategies are utilized to address real-world communication difficulties. The trial includes an individually tailored web application with native practice exercises and education materials that participants rehearse between treatment sessions. To evaluate whether treatment gains are relevant to the daily functions of the participant, outcomes are measured using a communication confidence rating scale and goal attainment scores. This method allows the targeting of individualized goals of high relevance to participants. In the future, transcranial stimulation could be combined with speech-language therapy to attain even more effective benefits [95].

Conclusions

Despite its relative rarity, PPA has led to conceptual advances in understanding the heterogeneity of dementia, the principles of selective brain vulnerability, and the neuroanatomy of the language network. PPA was arguably the first entity to show that there is more to dementia than memory loss, that the same clinical syndrome can be caused by multiple neuropathologies, that the same neuropathology can cause multiple syndromes, and that the relationship of syndrome to neuropathology is probabilistic rather than deterministic. Future work on PPA is likely to shed new light on the anatomical tropisms of neurodegenerative diseases and on the internal architecture of the language network.

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Measuring Behavior and Social Cognition in FTLD

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Introduction

Among neurodegenerative disorders, the frontotemporal lobar degeneration (FTLD) syndromes have a uniquely focal, and in some cases devastating, impact on socioemotional behavior. Because of this, research investigating the clinical neuropsychology of non-Alzheimer's dementias over the past 20 years has needed to expand beyond traditional cognitive domains like memory in order to accurately represent what are often the primary deficits in patients with FTLD. This requirement has occasioned many significant advances in the measurement of socioemotional behavior and cognition in patients with progressive cognitive deficits, while also revealing many unforeseen challenges.

Any investigation into behavior in the FTLD syndromes must start with an understanding of the neuroanatomic circuits affected by these diseases, and their contribution to healthy social and emotional behavior. While the FTLD syndromes have diverse and even somewhat individualized patterns of initial neuronal damage and spread, it has become clear that specific intrinsically connected networks (ICNs) [1] show distinct patterns of selective vulnerability in the different major neurodegenerative syndromes [2]. Predictably, the ICN initially impacted in typical Alzheimer's disease (AD) syndrome is the brain's network for performing memory operations (i.e., the default mode network, or DMN) [3, 4]. However, in behavioral variant frontotemporal dementia (bvFTD), it is an ICN underpinning salience-driven attention (the salience network, SN) [5], and in semantic variant primary progressive aphasia it is an ICN involved in both general and socioemotional semantic knowledge (the semantic appraisal network, SAN) [2, 6]. The realization that damage to the SN is both necessary and sufficient to create a catastrophic behavior syndrome in bvFTD patients has had a widespread impact over the past decade, not only on the study of the FTLD syndromes, but on the way social affective neuroscientists have understood normal salience-driven attention [7]. Similarly, as the FTLD community has consistently confirmed the existence of an overlapping but qualitatively different set of socioemotional impairments associated with svPPA syndrome, particularly when right frontotemporal circuits involved in the evaluation of semantic information become damaged [8–10], it has highlighted the central importance of the SAN for key socioemotional functions such as visceral emotional

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experience and expression, evaluating hedonic signals, and decoding social and emotional cues [11, 12].

Using Behavior to Evaluate Key FTLD Brain Circuits

Because the primary utility of neuropsychological testing in the FTLD syndromes is to identify and diagnose patients, and to mark the degree of disease progression, the best neuropsychological tests are those that reflect the functional integrity of these circuits that are specific to FTLD. Measurement is complicated by the cognitive deficits, loss of insight, and failure to cooperate fully with testing procedures that are typical of patients with these syndromes; thus, the best tests ideally show some degree of robustness and domain specificity in reflecting the intended circuits despite these obstacles. FTLD researchers have examined many such tests over the past two decades; while the majority of tests purporting to show specific brain–behavior relationships have been validated using structural MRI data reflecting neurodegenerative atrophy as a measure of brain circuit damage [13–15], investigators are increasingly showing correspondence of such tests to functional connectivity in these networks [5, 16, 17]. This is a particularly welcome advance, not only because such tests will be more sensitive in patients in the earliest stages of neurodegeneration before frank atrophy can be discerned, but also because there is substantial evidence that bvFTD-type behavior deficits may emerge as a result of a "disconnection syndrome" affecting these FTLD-specific circuits, both in patients with a more "subcortical" variation of bvFTD with little cortical involvement [18], and also in patients with other FTLD syndromes such as Progressive Supranuclear Palsy (PSP) [19].

Socioemotional deficits in the FTLD syndromes must be conceptualized as encompassing two distinct targets that are evaluated through very different measurement approaches: (1) socioemotional behavior or reactivity, and (2) socioemotional cognition or information processing. The first category, socioemotional behavior, includes all the physiological and behavioral *responses produced by the patient* in a socioemotional context or simply when presented with socioemotional stimuli. Typically, FTLD researchers investigating altered reactivity in patients with the FTLD syndromes have relied on precision laboratory approaches such as standard psychophysiological measurement and detailed observation and behavioral coding [20–23], including facial and vocal emotion coding [24, 25]. Increasingly, task-based fMRI studies are also being used to directly quantify altered patterns of neural response in FTLD patients. These measurement approaches have the benefit of scientific rigor and reproducibility, but also require special equipment and sophisticated user training for data collection and analysis, thus are suited only to research investigations and cannot easily translate into neuropsychological assessment approaches for patient identification and classification in broad clinical or even clinical trial settings.

A more holistic but imprecise measurement of FTLD patient behavioral responsiveness is also performed via observational methods such as home visit-based ethnographic coding and real-world challenge paradigms [21], which again require sophisticated training and cannot scale up for clinical use, but may be less equipment -heavy. Clinician quantification of spontaneous behavior during patient visits [26, 27] is a less precise but more scalable quantitative option. A fourth approach to documenting patients' holistic socioemotional responsiveness that has been widely used with FTLD patients is interview- or questionnaire-based informant reports on the patient's typical behavior, attitudes, and personality [10, 28–31]. These require little to no specialized training for data collection and have published normative reference sets available for interpretation, thus are accessible options for clinical and clinical trial use, though of course they lack the precision afforded by laboratory-based observational measures.

The second main category of socioemotional measurement in the FTLD syndromes is the more traditional measurement of social cognition, or more specifically, whether or not the patient is able to *identify and discriminate socioemotional stimuli and make correct interpretations of social*

scenarios. Based in the tradition of neuropsychological assessment of cognition, this approach emphasizes direct face-to-face testing of the patient's abilities, evaluating whether the patient is able to achieve a test score at a normal threshold. The most obvious and widely used example of this in the FTLD field is testing whether a patient can accurately discriminate or name emotional faces from static pictures or videos, though investigators have developed or adapted many tests evaluating socioemotional cue detection and interpretation of social scenarios [15, 32, 33]. This category of assessment is often idealized because theoretically it represents the most practically useful balance between precise but equipment-heavy laboratory approaches and more holistic but nebulous informant-based observational measures, in part because a precedent has already been set for performing neuropsychological evaluations with Alzheimer's disease patients both in clinical trials and at clinic, thus direct socioemotional testing has the potential to be rigorous yet still scale up for general use. However, the direct-testing approach for evaluation of social cognition in the FTLD syndromes has met with a number of important pitfalls that have limited success in this area, despite substantial effort being expended to develop and validate such tests.

The most obvious caveat to the value of these face-to-face tests of socioemotional functioning is that they are limited to the cooperativeness and cognitive ability of the patient, and thus become invalid measurement tools once a patient becomes behaviorally disordered enough that they refuse to participate or fail to engage appropriately with the testing situation, a reaction that often occurs only a year or two after initial presentation in the bvFTD patients for whom this testing is most important, that is, at a merely intermediate stage of disease progression. A core deficit in bvFTD, corresponding to its primary selectively vulnerable ICN, the salience network, is an early and progressive loss of the ability to care about meeting expectations in social situations, of which test-taking is a clear example. Thus, paradoxically, the most relevant socioemotional brain network to test in these patients is the one for which moderate dysfunction creates invalid test performance, logically limiting the utility of any face-to-face test for measuring SN progression. Furthermore, the SN is involved in attending and responding to stimuli that are personally and emotionally salient to the individual, thus early deficits are likely to appear as a highly personalized and focal failure to notice or care about a specific event or person in the course of daily life. Thus, at earlier phases of disease progression, these deficits can be difficult to evoke or observe during a homogenous, standardized testing situation, limiting the value of face-to-face testing for early detection of SN involvement. Finally, investigation of the range of normal intrinsic functional connectivity in healthy individuals over the past decade suggests that there is substantial normal inter-individual variability in SN function among healthy individuals [16, 17], corresponding to an equally wide range of normal socioemotional functioning. This means that, unlike a typical "achievement" test of memory or language functioning, where healthy individuals demonstrate a fairly narrow range of premorbid ability and thus cognitive deficits are easy to ascertain, it will not be initially apparent whether an individual's score on a test of SN function represents a relative deficit (i.e., a decline from premorbid functioning) for that individual, or is simply a reflection of lifelong weakness in the socioemotional domain.

While "achievement" in relation to the SN is exceedingly difficult to test in a valid face-to-face manner, direct patient testing of socioemotional abilities related to SAN function has been marginally more successful. In particular, a number of tests measuring comprehension of social and emotional semantics have been developed and validated for use with FTLD patients, and have been particularly effective at identifying the subset of bvFTD and svPPA patients who have right frontotemporal dysfunction [15, 34–37]. Some more difficult tests seem to be sensitive to early neurodegenerative dysfunction [38], though patients with semantic loss quickly hit the psychometric floor of such tests. As with neuropsychological tests measuring any cognitive domain, however, a patient's performance can be confounded by cognitive deficits in other domains or by dysfunction in correlated ICNs. For example,

the impact of generalized, non-social semantic deficits must be accounted for with any test purporting to measure comprehension of specifically socioemotional semantics. Emotion naming tests that provide labels and ask the patient to select among them rather than asking them to spontaneously label the emotion may be more accurate with FTLD patients.

Finally, a last challenge to socioemotional testing in the FTLD syndromes has been the need for tests to be valid for use in multicultural contexts across international boundaries. While cultural and linguistic influences are important when translating tests in traditional neuropsychological domains like memory and executive functioning, the interpretation of whether a socioemotional behavior is normal or abnormal is wholly dependent on the cultural context of the patient, making many such measures completely culturally invalid despite correct linguistic translation. While formal tests of patients' ability to recognize basic socioemotional cues such as facial emotions are marginally more cross-culturally robust, tests of higher order comprehension of social stimuli, and the expressive social behavior of the patients themselves, are often subject to very different rules governing social context and expectations. Thus far, the most effective response of the worldwide FTLD community has been for clinical researchers to design and validate sets of socioemotional measures within their own cultural context. This results in customized, local, and thus more accurate, socioemotional testing; however, this approach is extremely time intensive and inefficient, and leaves out countries and cultures without investigators focused on developing such tasks. While independent suites of effective socioemotional tests have been developed and validated for use with FTLD syndrome patients in North American, European, and Australian/New Zealander English-speaking contexts, as well as for South American Spanish-speaking patients [39–42], work is only beginning to develop such culturally valid batteries in Chinese- or Hindi-speaking patients. Individual groups in Europe have also developed and used socioemotional tests in non-English-speaking FTLD patients [43], and the GENFI study in Europe is currently developing and validating a set of socioemotional tests for use across its more than 10 linguistically distinct countries. Furthermore, even within linguistically similar groups, important cultural differences in social norms and expectations can substantially influence testing, further confounding the question of whether certain behaviors or test results reflect clinically abnormal socioemotional behavior. Using a patient as their own control over time to detect declines from baseline could partly mitigate these issues from a research design perspective; however, it is clear that development of cross-cultural evaluation methods for socioemotional functioning is a critical, ongoing need in the FTLD community.

Practical Socioemotional Testing in FTLD

The following is a discussion of a number of practical tests of socioemotional functions validated for use in FTLD patients and which have no major equipment or training requirements, thus have the potential for broader adoption either in clinical trials or in clinic. Rather than attempting to provide a comprehensive review of all such tests, the following section takes this opportunity to provide a more in-depth discussion of both published and unpublished data on a number of tests developed and validated by our group, with which we are of course most familiar. For some of the socioemotional functions discussed, there are additional valid alternatives developed by other investigators that are currently being used with FTLD patients, which can be found in the literature should the reader be interested in further study of these measures.

Measures Reflecting Salience Network Dysfunction in FTLD

As described earlier, the network most central to the bvFTD syndrome is the cingulo-insular-subcortical SN [44–46], a network that integrates sensory stimuli with interoceptive, hedonic, affective, and motivational information via the

anterior insula (AI), and which works to adjust attention and emotional arousal on the basis of the relevance of these signals. Subcortical SNnodes providing interoceptive signals include the dorsomedial thalamus, hypothalamus, amygdala, and midbrain periaqueductal gray (PAG) [5], and a node in the anterior cingulate provides motivational and top-down regulation in the SN [47, 48]. Because the SN is the hub of selective vulnerability in bvFTD, tests that are sensitive and specific to SN dysfunction are the most ideal measures for use in detecting and monitoring progression of the bvFTD syndrome. For the reasons explained earlier, face-to-face patient tests of the SN have been elusive, but a number of observer-based behavioral measures have been successfully validated as both sensitive and specific to SN dysfunction.

Revised Self-Monitoring Scale (RSMS). One of the measures most extensively validated for use in FTLD patients, and for which there is strong support for its correspondence with salience network structure and function, is the RSMS [49]. With neurodegenerative disease patients, this 13-item questionnaire has primarily been used as an informant-reported observational measure of the patient's typical spontaneous behavior in real-life social settings. The RSMS has been thoroughly validated for use in other non-neurodegenerative populations, and has good psychometric characteristics, including strong internal consistency and test–retest reliability [50, 51] as well as appropriate construct validity to predict related traits such as social anxiety and sociability [52]. It measures sensitivity and responsiveness to subtle emotional expressions during face-to-face interactions. Sample items include "In conversations, the patient is sensitive to even the slightest change in the facial expression of the other person they are conversing with," and "In social situations, the patient has the ability to alter their behavior if they feel that something else is called for."

The RSMS has been used in a number of studies with neurodegenerative disease patients, and seems to be particularly sensitive to the core social deficits inherent to bvFTD syndrome. Multiple studies have shown that not only do bvFTD patients score abnormally low, but they also are rated as having worse social sensitivity than patients with other syndromes such as svPPA, PSP, or AD [13, 17, 53] (Fig. 1). Importantly, there is strong evidence for the correspondence of RSMS score to structural integrity of the SN. In one study, Shdo et al. (2017) [13] examined 275 individuals with bvFTD, svPPA, nfvPPA, PSP, and AD, as well as healthy older controls, and performed a voxel-based morphometry whole-brain analysis to discover linear relationships between RSMS score and structural gray matter volume regardless of syndromes. They found that RSMS score predicted volume in medial and lateral temporal as well as inferior frontal structures, and found that subcortical structures including the amygdala, thalamus, caudate, putamen, and globus pallidus corresponded with RSMS. RSMS score has also been correlated with white matter integrity measured via DTI analysis. Examining 145 participants, including 105 patients with bvFTD, svPPA, and nfvPPA as well as 40 healthy controls, Toller et al. (2020) [54] used TBSS to perform a voxel-wise analysis of whole-brain white matter tracts to determine how white matter FA was predicted by RSMS score. Higher RSMS score was significantly associated with higher FA values in the right uncinate fasciculus (UF), a white matter structure that connects the anterior temporal lobe with inferior frontal regions. This effect was not only found in the entire sample (patients plus controls), but was also found to be significant in the subset of 40 healthy controls alone, suggesting the RSMS is sensitive not only to disease-related social deficits, but also mild normal variations in white matter structural integrity in the right UF. Patients with bvFTD and svPPA both had significantly lower FA in the right (M ± SD; bvFTD: 0.35 ± 0.01; svPPA: 0.36 ± 0.01; NC: 0.41 ± 0.01) and left (bvFTD: 0.34 ± 0.01; svPPA: 0.33 ± 0.01; NC: 0.39 ± 0.01) UF compared to NCs, though neither right nor left UF integrity was abnormal in patients with nfvPPA. This study also found an interesting dissociation between svPPA and bvFTD patients in terms of contribution of right frontotemporal gray matter volume versus white matter integrity

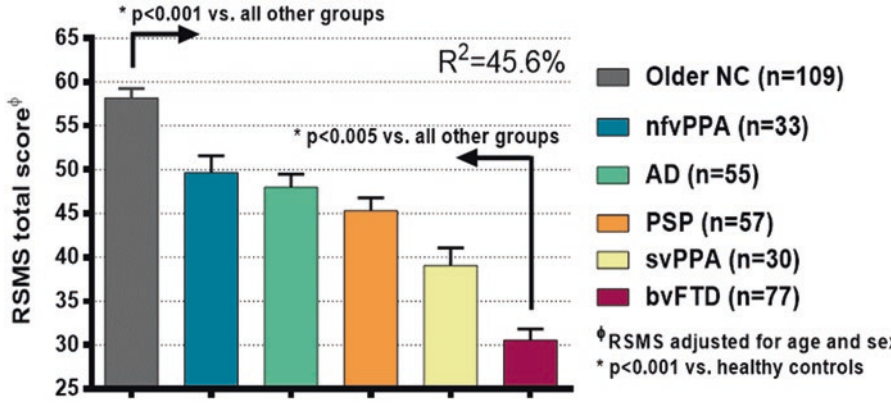

Fig. 1 The RSMS (Revised Self-Monitoring Scale, Lennox and Wolfe [49]) shows high accuracy differentiating bvFTD patients from healthy older controls and from all other FTLD syndromes and AD

of the UF to RSMS score. Though FA in the UF did not significantly predict RSMS score in the bvFTD group alone, lower gray matter volume in the right medial OFC ROI did. Thus, though right UF integrity alone was able to predict socioemotional sensitivity in both healthy controls and svPPA syndrome patients, in patients with bvFTD gray matter volume in the right medial OFC cortex adjacent to the UF tract predicted socioemotional behavior than UF integrity.

Perhaps the strongest evidence for the value of using informant-reported RSMS to reflect SN integrity comes from studies directly linking RSMS score with functional connectivity in the SN. In a study of 168 participants, including patients with bvFTD, svPPA, nfvPPA, PSP, and AD syndromes, and healthy controls, Toller et al. (2018) [17] found that higher functional connectivity in the SN significantly predicted higher RSMS score, even controlling for atrophy and for diagnostic group membership. Region-of-interest analysis of connectivity within the SN showed that RSMS score could be predicted by connectivity among cortical structures (bilateral AI and ACC), as well as between the right AI and subcortical structures. Not only did this result occur across the whole sample, but, in a second analysis of a subsample of 98 healthy controls across the age spectrum (age range 19–87), RSMS score showed this same significant linear relationship, again suggesting that RSMS score not only reflects disease-related social insensitivity caused by damage and dysfunction in the SN, but it actually reflects normally occurring individual differences in socioemotional sensitivity in a manner specific enough to reflect normal SN connectivity.

Finally, the longitudinal sensitivity of the RSMS to disease progression in bvFTD patients has also been established, using a large multi-site cohort of 475 participants who had behavioral Mild Cognitive Impairment, bvFTD, or were asymptomatic controls (Toller 2020) [53]. This study showed a main effect of disease severity (measured by CDR® plus NACC FTLD score) in which RSMS decreased significantly at every disease stage as CDR worsened. Linear mixed effects models showed a significant main effect of disease duration in which RSMS decreases linearly in patients at a rate of 5 points per year (average RSMS slope per year: -2.13 ± 1.29) in bvFTD. An additional voxelwise analysis of structural brain volume showed that more rapid declines on the RSMS were associated with faster progression of gray matter atrophy in regions of the SN and SAN, including the right AI, dorsal ACC, and OFC. Sub-regional analysis by disease progression showed some evidence that worsening score on the RSMS tracks with loss of volume in the thalamus, primarily in very mild and mild disease stages, but to a lesser degree later in the disease. This study also examined whether the RSMS was able to differentiate between mutation carriers and non-carriers, though no

differences were found. This study also used the Zarit Burden measure to show that worse RSMS score predicts greater self-reported burden for bvFTD caregivers, which provides evidence that the loss of socioemotional sensitivity measured by the RSMS reflects a clinically meaningful symptom in FTLD patients, an important consideration for its potential inclusion as a clinical trial outcome measure.

Interpersonal Adjectives Scales – Warmth Subscale (IAS-Warmth). Another measure for which there is solid evidence that it reflects SN function is the Warmth subscale of the IAS [55]. The IAS has been used with FTLD patients as an informant-reported personality questionnaire designed to measure trait-level expression of interpersonal characteristics, including dimensions of dominance and affiliation. Informants rate on an 8-point Likert scale the degree to which patients can be accurately described using a list of adjectives descriptive of an interpersonal behavior (e.g., "self-assured"; "shy"; "iron-hearted"). The IAS as a whole produces ratings of 8 traits: dominance, arrogance, coldness, introversion, submissiveness, ingenuousness, warmth, and extraversion. Numerous studies of its characteristics in FTLD patients have been published, which include evidence that depending on their syndrome, patients show characteristic changes in personality [56], that these changes correspond with neuropsychological features [57], and that patients with the most significant personality changes, i.e., those with bvFTD and svPPA, are least likely to be aware of those personality changes [58]. Studies have also demonstrated the unique patterns of atrophy corresponding with different IAS facets [59].

While a number of IAS facets appear to change with FTLD, one dimension in particular seems to correspond with SN structure and function, the Warmth–Coldness axis. One study of the structural gray matter correlates of the IAS included 239 individuals, comprised of patients diagnosed with bvFTD, svPPA, nfvPPA, corticobasal syndrome, PSP, and AD syndrome, as well as healthy controls [59]. Warmth scores were significantly lower in the bvFTD and svPPA groups, and the scores for their opposite trait, Coldness, were significantly higher than in NCs, though this effect was not seen in any of the other neurodegenerative disease syndromes. Warmth score correlated with primarily right-sided structures reflecting SN and SAN regions, specifically the gray matter volume in predominantly right frontal and anterior temporal lobe structures, including the right posterior caudal orbitofrontal cortex, the right anterior and medial insula, the subgenual cingulate region, the anterior medial prefrontal cortex, the right caudate head, the anterior parahippocampus and hippocampus, amygdala, and superior temporal pole. This apparent correspondence of IAS-Warmth with both SN and SAN, however, was further clarified in another study directly examining the relationship between IAS-Warmth and functional connectivity. Toller et al. (2019) [16] studied 132 participants, including healthy controls and patients with bvFTD, svPPA, nfvPPA, and AD. Their analysis showed that while all patient groups had significantly lower IAS-Warmth scores than NCs, only the bvFTD group scored outside of the normal range (−2 SD below average), while the other patient groups averaged less than 1 SD below average (*T*-score ± SD; bvFTD: 31.1 ± 2.7, AD: 46.65 ± 2.3, svPPA: 42.3 ± 2.8, nfvPPA: 47.73 ± 2.6; NC 56.3 ± 2.5). They found a significant interaction between diagnostic group and time (premorbid versus current IAS-Warmth) showing that patients with bvFTD ($p < 0.013$) and svPPA ($p < 0.013$) had significant declines from premorbid to current warmth compared to the NC group. When they investigated whether current functional connectivity in the SN, SAN, or DMN predicted current warmth score across the entire sample (controls and patients), only higher connectivity in the SN predicted higher current IAS-Warmth score after atrophy correction, and SAN connectivity dropped out of the model, suggesting that SN connectivity was the primary driver of IAS-Warmth score. The study furthermore documented the divergence across different patients within the bvFTD and svPPA groups in the degree of change they experienced in both warmth and SN connectivity from estimated premorbid to current levels. SN connectivity did not predict IAS-Dominance, thus

connectivity in this network appears to be specific to warmth. Overall, these studies suggest that interpersonal warmth is a trait characteristic that decreases in many patients with the FTLD syndrome, and that it acts as an index of the degree of decrease in SN connectivity in those patients.

Measures Illustrating the Gating Mechanism of the SN in Socioemotional Behavior

Evidence has accrued from numerous sources that the SN plays a role in activating certain downstream networks [60], and this influences higher order social cognitive processes like moral reasoning [61] and theory of mind [62] that predominantly rely on those downstream ICNs [63], particularly the DMN and the frontoparietal adaptive task network (FPN) [64]. Studies using these kinds of complex socioemotional tasks with FTLD patients suggest that bvFTD-related SN dysfunction directly impacts their decision-making, likely through the mechanism of altering patients' ability to notice salient cues while processing complex, often multimodal information from the realistic scenarios these tasks often employ. Patients with most neurodegenerative syndromes, including AD, show nonspecific impairments on these types of difficult face-to-face tests because of their complexity and reliance on multiple cognitive functions [33, 62], thus they are not useful for differential diagnosis or for isolating SN dysfunction; however, in FTLD patients, scores often do correlate with SN structure and function, thus they may have some utility for early detection.

Chiong and colleagues [61] performed a moral reasoning task during task-based fMRI with healthy older controls and 13 early bvFTD patients, and found not only that bvFTD patients tended to respond to scenarios in a more utilitarian manner but also that this tendency was directly explained by differences in the way bvFTD patients activated the underlying networks. When healthy controls deliberated about moral scenarios where personal relationships often supersede practical logic, SN activation led to activation of the DMN; however, in the early bvFTD patients, the SN failed to exert this downstream influence on the DMN, and instead the FPN was more likely to activate, resulting in decisions that relied on logical rather than personal considerations.

This same relationship has been found when FTLD patients are asked to perform complex social reasoning and make "theory of mind" inferences from realistic social scenarios. One direct face-to-face task that has been used in a number of studies of FTLD patients to test this ability [15, 33] is The Awareness of Social Inference Test (TASIT)–Social Inference Enriched subtest (SI-E) [65]. This test has shown differential diagnostic utility in discriminating bvFTD-specific socioemotional deficits in comparison to patients with the aphasia syndromes or AD, and has even shown sensitivity to social reasoning deficits in PSP [33]. This subtest of the TASIT consists of 16 short video vignettes in which either a visual or verbal enrichment is given to provide unambiguous cues about the social situation, the state of knowledge of each character, and the characters' social intentions. After watching each video, four questions related to what the characters in the video do, think, say, or feel are used to assess the patient's understanding of the social interaction they just viewed. To correctly interpret the videos, realistic contextual and paralinguistic cues have to be selectively attended to and integrated, which makes the TASIT-SIE an appropriate tool to measure the patient's ability to make ToM social inferences from complex dynamic multimodal information in real life. While the ecological validity of this test, and by extension its ability to reflect real-life impairments, is its strength, the drawback is that, to correctly interpret a scenario, patients must successfully perform many complex social and non-social cognitive operations, thus task failure may be due to problems with memory, executive function, language, or visuospatial functioning, not necessarily due to deficits in socioemotional processing per se. This makes the test, and all other complex social cognition tests like it, nonspecific for differential diagnosis among the

FTLD syndromes because patients from many groups underperform or fail [33].

However, the TASIT-SIE has been used to model how SN damage in FTLD patients can create a powerful cascade effect in which patients are unable to make incorrect social inferences even when other brain networks required for theory of mind are intact. In that study, Rijpma and colleagues [62] performed the TASIT-SIE with a total of 179 participants, including patients with bvFTD, PSP, and AD syndromes. They examined how gray matter volume in three ICNs, the DMN, FPN, and SN, influenced patients' ability to infer others' intentions using the TASIT-SIE, and found that while lower volume in all three networks appeared to predict poorer social reasoning, when all three networks were included in the same model, task performance was entirely accounted for by SN volume and not by DMN and FPN volume. While numerous other studies have found that theory of mind reasoning is typically performed by the DMN and FPN, this study used the realistic video vignettes of the TASIT-SIE to further confirm the SN gating hypothesis, showing that if a patient is unable to recognize and selectively attend to key socioemotional cues while viewing a complex scene due to SN damage, then they cannot successfully engage the DMN and FPN to perform downstream social cognitive operations.

Measures Reflecting Semantic Appraisal Network Dysfunction in FTLD

While the SN is of central importance in understanding the socioemotional deficits in the FTLD syndromes, a second intrinsically connected network is also responsible for many of the severe symptoms we associate with FTLD. As described earlier, the SAN appears to be selectively vulnerable not only in the svPPA syndrome, but also in a large proportion of patients with bvFTD [18]. A seed placed at the medial boundary of either temporal pole reveals a normally occurring ICN that includes both medial anterior temporal and subgenual cingulate cortex, as well as the head of the caudate, the nucleus accumbens, and the amygdala [2, 35, 66, 67]. The functions of this network are less well understood, but FTLD patients with early and focal damage to this network have a disproportionate number of deficits reading emotions and other social cues, even compared to other bvFTD patients, and are more likely to be described as having social disinhibition (i.e., rudeness) during the first year of their disease [18, 37]. Recent work suggests that these socioemotional symptoms may reflect disruption of the inferior orbitofrontal/basal ganglia structures that facilitate hedonic evaluation, and their links to anterior temporal areas involved in semantic knowledge [35]. Tests that reflect the ability to make judgments about socioemotional semantics, including emotion and social cue identification, seem to provide the best reflection of SAN function, though a more thorough investigation of this connection is still needed in the FTLD field.

Tests of Emotion Reading: Numerous studies of emotion reading ability in patients with the FTLD syndromes have been published, using a variety of testing modalities and stimuli. While these measures are typically direct, face-to-face patient tests, they have included measures of facial, vocal, and bodily expression of emotion, both static (picture) and dynamic (video clip) stimuli, single modality versus multimodal, as well as full expression versus degraded or morphing gradations of emotion. A number of commonalities have arisen out of these studies that can provide guidance for using these measures in patients with the FTLD syndromes. First, the identification of emotion reading impairments in patients is confounded by the fact that there is a wide range of emotion reading ability among healthy individuals, thus a "low average" score on a test could be a normal, unchanged performance for one patient whose premorbid capacity for emotion reading was always low, while it could represent a substantial deficit for another patient whose premorbid ability was high. Emotion tests that are particularly difficult, such as those requiring fine-grained distinctions of facial affect, or those requiring affect reading with complex or low signal-to-noise stimuli, are

particularly problematic to interpret for these reasons, as dementia patients rapidly approach an impaired threshold on these tests, often hitting floor levels early in the disease process [68]. Tests placing a high demand on non-emotional systems, such as auditory processing for prosody tests, visuospatial processing for facial emotion tests, or semantic processing for tests where fine distinctions among emotions must be spontaneously labeled, can result in test failure despite intact emotion systems. For these reasons, even with unambiguous stimuli designed to realistically reflect real-life emotion reading ability, patients without emotion system dysfunction, such as patients with AD syndrome, may perform just as poorly as patients with bvFTD or svPPA, making these tests imprecise for differential diagnosis in FTLD.

However, when understood as a window into regional neural dysfunction, emotion reading tests do have some clinical utility. One test that has been used in studies with FTLD patients is another subtest of the TASIT, called the Emotion Evaluation Test (EET), which consists of 28 videos of about ~20-second duration in which actors express emotions through congruent facial, vocal, and gestural modalities using realistic but semantically neutral scripts. Patients are asked to select the correct label for the video from among the six basic emotions (happy, sad, disgusted, surprised, angry, frightened, plus neutral). One benefit of these stimuli is that they are realistically dynamic (i.e., video based) and multimodal (with multiple, congruent cues of the emotion), thus are undemanding enough that patients with non-social cognitive deficits are less likely to fail them due to difficulty processing the stimuli, yet they still detect true emotion reading impairments. Patients with bvFTD and svPPA both perform more poorly than AD patients on the TASIT-EET [15, 18, 68]. Studies examining the gray matter correlates of the test show broad correspondence with bilateral temporal lobe structures, as well as inferior frontal cortex [15, 69].

Another similar but freely available test that is increasingly used with FTLD patients is the Dynamic Affect Recognition Test (DART). This shorter measure is a video-based test comprised of 12 20-second vignettes of an actor expressing one of the six basic emotions (happy, surprised, sad, angry, fearful, disgusted) via ecologically realistic and congruent facial, vocal, and postural cues, and with semantically neutral scripts. Each vignette involves only one actor, whose facial emotions were coded via the Facial Action Coding System (FACS) [70] to ensure valid and reliable emotional expression. One study [71] compared FTLD patients' performance on the DART, the TASIT-EET, and a third static facial emotion test, the Affect Matching subtest of the Comprehensive Affect Testing System (CATS-AM) [72]. The study examined emotion identification performance on the three tasks with 153 participants, including patients with bvFTD, svPPA, nfvPPA, PSP, and AD, along with older healthy controls. ROC modeling comparing all three tests showed they had similar sensitivity discriminating bvFTD patients from healthy controls (AUC: DART = 0.94; TASIT-EET = 0.91; CATS = 0.81). A VBM analysis of gray matter showed that DART score had a linear relationship with volume in the left superior medial temporal pole, left medial temporal pole, left inferior temporal pole, left hippocampus, left caudate head nucleus accumbens, right caudate head/nucleus accumbens, right dorsal anterior insula, and the right anterior inferior temporal gyrus. When the DART was analyzed controlling for patients' semantic loss, in order to model emotion reading distinct from any language deficits that might interfere with their ability to correctly label the videos, the resulting VBM revealed primarily right-sided structures, retaining insula and caudate/accumbens regions, while correlations with ventrolateral temporal regions did not appear. Overall, the TASIT-EET and the DART appear to function similarly in patients with the FTLD syndromes, and reveal very similar structural anatomic substrates in ventral frontal and temporal regions.

Another recent study [69] examined the functional correlates of the TASIT-EET, and demonstrated more conclusively the correspondence of these emotion reading tests with SAN function rather than SN or other brain networks. In this study, a total of 185 individuals were

studied, including patients with bvFTD, svPPA, nfvPPA, PSPs, and AD, along with older healthy controls. As expected, they found that patients with bvFTD and svPPA had significantly lower TASIT-EET scores than controls. However, they also modeled TASIT-EET score against functional connectivity in the SN and SAN ICN, and found that when SAN and SN were modeled together, mean connectivity in the SAN independently predicted TASIT-EET scores but the SN did not, when SAN was accounted for, and this strong relationship with SAN connectivity remained after atrophy correction and error checking for the confounding effects of diagnostic group membership. ROI-level analysis showed that connectivity between the right anterior temporal pole and other parts of the SAN, including regions of the subgenual cingulate involved in making hedonic evaluations, was primarily responsible for differences in patients' performance on the TASIT-EET. Overall, these results suggest that though these video-based emotion labeling tests seem to correspond with general frontotemporal anatomy in FTLD syndrome patients, the functional anchors for test performance are the right temporal pole and the medial orbitofrontal cortex, regions located in the SAN and which are selectively vulnerable in a subset of patients with FTLD.

Tests of Socioemotional Semantics. Another aspect of socioemotional cognition that deteriorates in patients with some variants of FTLD is the knowledge of social rules, expectations, categories, and concepts. This symptom often becomes specifically associated with a "right temporal" syndrome of bvFTD or svPPA [34, 36, 73], though it is actually an element of many bvFTD or svPPA patients' socioemotional behavior deficits. Many FTLD clinics administer informal tests of "famous faces" to determine if a patient's semantic knowledge about individuals they should know is intact, though these tests are notoriously difficult to standardize because they rely on culturally specific knowledge of famous individuals from different historic epochs.

Another approach to evaluating socioemotional semantics is to directly test patients' knowledge of social information. One test that has been designed and validated for FTLD patients is the Social Norms Questionnaire (SNQ) [74, 75], a set of 22 yes–no questions asking patients whether specific social behaviors are appropriate. The measure contains two subscales, one control scale (*Overadhere*) with items describing appropriate behaviors (e.g., "Is it socially acceptable to tell someone your age?"), and the test scale (*Break*) with items describing inappropriate behaviors (e.g., "Is it socially acceptable to spit on the floor?). The test was initially validated using data from 200 well-educated neurologically healthy predominantly Caucasian controls aged 45–90 to confirm response agreement was over 90% for all items. A study [75] of the differential diagnostic utility of the test with 283 patients, including those with bvFTD, svPPA, nfvPPA, PSP, CBS, and AD, showed that only bvFTD and svPPA patients had significantly higher Break norms errors than controls, even though additional patient groups (PSP, nfvPPA, and bvFTD) made significantly more Overadhere control task errors than the healthy group. VBM analysis showed that SNQ score had a strong linear relationship with gray matter volume in right>left anterior temporal lobes as well as inferior frontal regions and the head of the caudate. Thus, the Break subtest of the SNQ appears to be specific to the socioemotional semantic loss of bvFTD and svPPA patients, and corresponds with structural anatomy found in the SAN.

Another newer test of socioemotional semantics, designed for use with FTLD patients but modeled on non-social tests of semantic knowledge like the Peabody Picture Vocabulary Test (PPVT) and the Pyramids and Palm Trees test (PPT), is the Social Interaction Vocabulary Test (SIVT). This 18-item test examines patients' ability to understand and label interpersonal dynamics. It is designed as a multiple-choice picture/word socioemotional vocabulary matching task. Patients are given a word describing a specific socioemotional interaction (e.g., "consoling"), and then are asked to choose from among 4 pictures depicting two interacting individuals in order to identify the image that best represents the meaning of the word. Pictures are

carefully matched for visual complexity, body posture, and gestures of the actors, and are arranged with 3 subscales corresponding to easy, moderate, and difficult vocabulary words. The test was normed with 52 neurologically healthy, predominantly Caucasian and well-educated individuals aged 21–87, who performed at or near ceiling. When SIVT performance was examined in 213 individuals, including patients with bvFTD, svPPA, nfvPPA, PSP, CBS, AD, and healthy controls, only patients with bvFTD and svPPA had significantly lower total SIVT scores than healthy controls. A VBM analysis showed a linear relationship between SIVT score and both frontotemporal and subcortical structures known to be in the SAN, including right>left subgenual cingulate, temporal pole, and the nucleus accumbens and rostral caudate structures (Fig. 2). These results suggest that the ability to make these socioemotional associations is not only mediated by temporal structures known to convey semantic knowledge, but also dependent on ventromedial frontal-subcortical circuits involved in hedonic evaluation.

Conclusions

Numerous tests have been used to evaluate socioemotional behavior in FTLD patients, and most if not all of them are capable of revealing the impairments typical of bvFTD; however, the most useful tests are those that are sensitive and specific enough to reveal the dysfunction of the two key brain networks known to mediate the majority of socioemotional deficits in the FTLD syndromes: the salience and semantic appraisal networks. While SN integrity has proven difficult to test in face-to-face clinical encounters, questionnaire-based accounts of patient behavior from informants who are in a position to observe them well yield a surprisingly accurate reflection of individual differences in SN function. Socioemotional functions associated with the SAN are easier to evaluate through traditional patient-facing cognitive testing, and may include tests of emotion reading, and assessment of the vocabulary for social interactions and personal traits. Further progress needs to be made by the field toward refining and fully validating the various potential tests to precisely

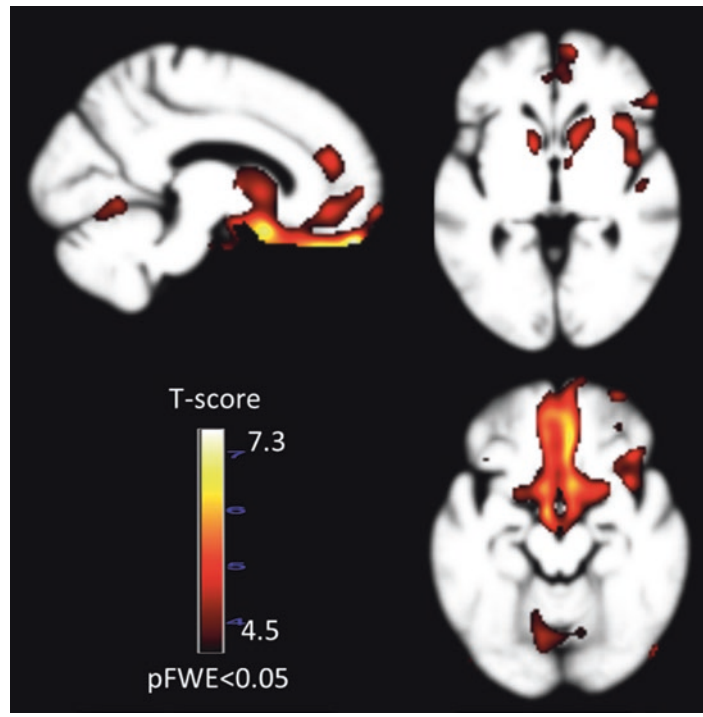

Fig. 2 SAN network gray matter correlates of the Social Interaction Vocabulary Task (SIVT). VBM analysis of regions of the brain showing a linear relationship between socioemotional semantic loss and volume loss in patients with neurodegenerative disease

evaluate socioemotional functioning in patients with the FTLD syndromes; however, it is clear that this set of disorders has provided the impetus for much more neuroscientifically rigorous evaluation of this cognitive domain than has previously been available in the field of clinical neuropsychology.

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Clinical Update on *C9orf72*: Frontotemporal Dementia, Amyotrophic Lateral Sclerosis, and Beyond

Dario Saracino and Isabelle Le Ber

Introduction

The last decades have marked a turning point in the knowledge of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), two diseases forming a clinical continuum and sharing common pathogenic mechanisms and genetic etiologies. In particular, the identification of the pathogenic GGGGCC repeat expansion in the first intron of the *C9orf72* gene, responsible for familial FTD and ALS, in 2011, represented a breakthrough discovery in these domains. Most healthy individuals in control populations harbor less than 24 GGGGCC repeats, and most often only two to eight repeats [1]. Although the exact pathogenic threshold remains uncertain, expansions above 30 repeats are usually considered pathogenic in most studies. However, the vast majority of patients carry much larger expansions ranging from several hundred to thousand repeats [1, 2].

The discovery of the *C9orf72* expansion led to strong scientific emulation and important advances, but the molecular and biological mechanisms by which the expansion might produce neurodegeneration are not completely elucidated. Three pathogenic mechanisms, not mutually exclusive, are proposed: (i) loss of function caused by reduced C9orf72 protein levels in brain, possibly mediated by methylation of a CpG island upstream to the expansion repeat [3], (ii) toxicity of mutant RNA that aggregates into nuclear foci, and (iii) accumulation of dipeptide-repeat (DPR) proteins generated by non-ATG dependent translation of the expanded repeat [4]. At the pathological level, the mutation is mostly associated with FTLD-TDP type A or type B subtypes, or with a combination of both [5, 6], together with widespread p62-positive inclusions, as well as intranuclear RNA foci and cytoplasmic DPR inclusions, the lesional signatures of *C9orf72* disease [7, 8].

The relevance of *C9orf72* expansion within the FTD/ALS spectrum is now well established [9]. In

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most countries, *C9orf72* represents the most frequent genetic cause of familial FTD (8–25%) and ALS (27–47%) and is the gene most commonly found in families with a combination of both disorders (65–80%) [1, 2, 9–12], although mutation frequencies vary according to specific demographic and geographic contexts. Notably, the prevalence of the expansion is significantly lower in Asian populations than in those of European and North-American ancestry [12, 13], both being different from intermediate frequencies in Indian populations [14]. It is also the most frequent genetic cause of "apparently sporadic" FTD or ALS implicated in 4–20% of patients without any family history of neurodegenerative diseases [1, 2, 9, 15, 16], suggesting that genetic testing should be proposed in apparently sporadic cases as well.

A decade after the discovery of *C9orf72*, several genetic and clinical questions remain unsolved. For example, the occurrence of an anticipation – at the clinical and molecular level – in *C9orf72* kindreds is still debated. There have been an increasing number of reports suggesting that the spectrum of *C9orf72*-related phenotypes is broader than the behavioral variant of FTD (bvFTD) and ALS, encompassing psychiatric disorders and, possibly, parkinsonian syndromes; however, the factors driving this variability are still unknown. The reliable cutoff for the pathogenic repeat number and the implication of intermediate alleles in FTD, ALS, or in other neurological phenotypes are still uncertain as well. All these questions have a significant impact not only in clinical practice for diagnosis and genetic counseling but also in a research context for the initiation of therapeutic trials. In this chapter, we will address all those issues and summarize the recent updates about clinical aspects of *C9orf72* disease, focusing on both the common and the less typical phenotypes.

Characteristics of *C9orf72*-related Frontotemporal Dementia

The behavioral variant of FTD is, by far, one of the most common phenotypes in *C9orf72* carriers. Patients carrying the expansion fulfill the possible and probable bvFTD criteria rather well, but the sensitivity is lower compared to neuropathologically confirmed bvFTD cohorts [17]. Overall, no specific cognitive and behavioral profile distinguishes *C9orf72* patients from other genetic or sporadic FTD cases [18]. However, specific cognitive domains might be altered early in the disease course since mild deficits in cognitive inhibition [19] and semantic access [20] have been evidenced in presymptomatic *C9orf72* carriers. As part of the clinical phenotype, a proportion of patients with bvFTD or FTD/ALS phenotype may develop parkinsonism occurring during disease course whose severity is milder than in other genetic or non-genetic FTD [18, 21].

The patterns of neuroimaging changes are distinctive according to FTD genotypes, and *C9orf72* patients have relatively symmetrical and diffuse volume loss [22] and variable rates of atrophy, with some patients progressing rapidly and others very slowly [22]. Multiple studies have shown early involvement of subcortical structures, such as basal ganglia, and hippocampus, amygdala [22–24], and thalamus as well [25]. Involvement of the cerebellum is seen particularly in patients with *C9orf72* mutations [26].

Overall, the mean disease duration is shorter in *C9orf72* (6.4 ± 4.9 years) than in other FTD genotypes, in particular *GRN* (7.1 ± 3.9) or *MAPT* (9.3 ± 6.4) [12]. This is partly explained by the deleterious impact of ALS, which shortens the survival of a proportion of *C9orf72* carriers. Besides, a particular subset of *C9orf72* expansion carriers have a remarkably different and slow progression corresponding to the "FTD phenocopy" syndrome. These patients exhibit behavioral and cognitive changes indistinguishable from those of typical bvFTD, but with remarkably slow progression [27–30]. They present only mild executive deficits and slow brain imaging changes, as illustrated in Fig. 1. Clinical and cognitive deficits remain relatively stable over time and the survival time may by longer than 20 years. Even if this repre-

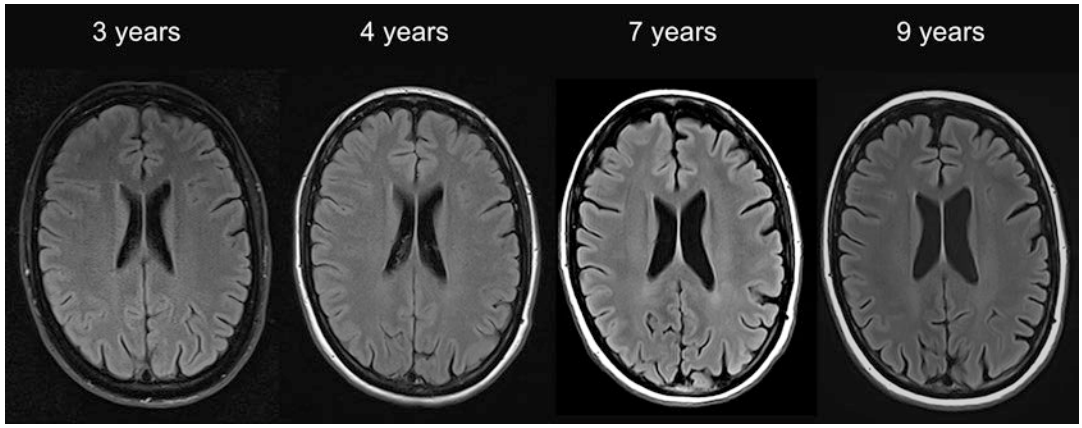

Fig. 1 Neuroimaging characteristics (brain MRI, axial sections) of a *C9orf72* patient with a slow progression evocative of FTD phenocopy. Follow-up over a 9-year disease duration

sents a possible phenotype in some *C9orf72* carriers, a recent review assesses that *C9orf72* expansion explains only a minority (less than 2%) of "FTD phenocopies" [31]. The predictors and the genetic/environmental factors contributing to the slow progression of neurodegeneration in these cases are not determined, but their identification will undoubtedly improve our knowledge on the mechanisms and disease modifiers implicated in *C9orf72* progression.

Characteristics of Amyotrophic Lateral Sclerosis Phenotypes Associated with *C9orf72* Expansion

In *C9orf72* carriers presenting with ALS, the disease has no particular distinguishing features; nevertheless, bulbar onset and co-occurring cognitive deterioration (56% of the patients) are overall more frequent with respect to non-mutated cases [11, 32, 33]. The *C9orf72* ALS population presented relatively more homogeneous clinical features than the non-*C9orf72* ALS population [34]. Disease duration is shorter in *C9orf72* than in other genetic forms of ALS [9, 32, 34, 35], and the *C9orf72* group included a significantly smaller fraction of slow-progressing individuals [34].

Psychiatric Symptoms in *C9orf72* Carriers: A Continuum with Frontotemporal Dementia and Amyotrophic Lateral Sclerosis

The high prevalence of psychotic symptoms in *C9orf72* families has highlighted the potential links and shared predispositions between FTD, ALS, and psychiatric disorders [10, 36–41]. Psychiatric symptoms or syndromes in *C9orf72* carriers variably include hallucinations (mostly auditory and visual), delusions (especially persecutory, jealousy, and grandiose delusions), and other psychotic (schizophrenia, bipolar disorder/hypomania) or obsessive-compulsive disorders. They are present in 10–50% of *C9orf72* patients according to the populations and may either occur concomitantly with FTD/ALS symptoms, or precede their onset by several years or decades. A large study in *C9orf72* kindreds underlined that family members of FTD or ALS patients also had increased risk of autism and other major psychiatric disorders, but the absence of genetic analyses in family members with psychiatric diseases was a limit of this study [40].

While there is now strong evidence supporting the association of psychotic symptoms with *C9orf72* expansion, the neuroanatomical substrate of those neuropsychiatric syndromes remains elusive. A functional deficit of the thal-

amus, detected at the early stage of *C9orf72* disease, does not appear to be specifically associated with psychotic symptoms [42]. Psychiatric symptoms in *C9orf72* rather correlated with a cortical and subcortical network implicated in schizophrenia including frontal, temporal, and occipital cortices as well as thalamus, striatum, and cerebellum [40, 43]. Interestingly, presymptomatic carriers showed abnormally low gyrification in left frontal and parieto-occipital regions, which was detected years before symptom onset [44]. Together, these findings provide the first clues to understand the neuroanatomical bases and networks implicated in *C9orf72*, but further investigations are warranted to fully elucidate their mechanisms, and further studies will clarify whether these abnormalities are part of a neurodevelopmental phenomenon.

Finally, the discovery of *C9orf72* gene has enlarged the clinical continuum linking FTD and ALS to psychiatric diseases. It led to reconsider the frontier between frontal behavioral and psychiatric disorders, as both are linked by similar molecular mechanisms and common functional network alterations in *C9orf72* carriers. Besides defining new exciting links between neuro-psychiatric disorders, this also raises new important questions that should be considered in clinical practice. First, the recommendations of genetic analysis in patients from *C9orf72* families presenting with psychiatric symptoms need to be clarified. More broadly, it opens the questions of the indications, criteria, and limitations of genetic analyses that could be proposed to patients suffering typical or atypical psychiatric diseases, outside of a familial context of *C9orf72* mutation [45]. These relevant questions must be addressed in the context of international consortia of experts in FTD, involving psychiatrists and geneticists too, in order to provide a framework and guidelines defining the indications and limitations of genetic testing in these patients.

Primary Progressive Aphasias Are Rare Phenotypes in *C9orf72* Patients

Unlike bvFTD, primary progressive aphasias (PPAs) are rarely associated with *C9orf72* expansion, as shown by the low frequency (1%) of *C9orf72* mutation carriers in a large North-American population of 403 PPA patients [46] and in other studies [16, 21, 36, 47]. Only few cases of *C9orf72*-related PPA have been described in detail in the literature [46, 48, 49]. Their phenotypes were mostly consistent with non-fluent and semantic PPA variants [12, 46]. Furthermore, a large European-Canadian study evidenced an important discrepancy between *C9orf72* and *GRN* genotypes, as only 3% of 1433 *C9orf72* included in this study have initially presented PPA, compared to 14% of *GRN* carriers [12]. This suggests that gene-specific effects lead to selective vulnerability of brain structures that differentially affect language networks. Further studies should clarify the biological determinants of selective lesion tropism for the language networks in genetic patients displaying PPA.

Implication of *C9orf72* in Dementia Syndromes Other than Frontotemporal Dementia

An association of *C9orf72* with Alzheimer's disease (AD) has also been examined. Episodic memory disorders at onset, mimicking Alzheimer's disease, are rarely associated with *C9orf72* expansion [16, 50–53]. Several studies have detected expansions in clinically diagnosed or pathologically confirmed AD patients, with a low prevalence accounting for less than 1% of AD populations [54, 55]. Although rare, this association has suggested a possible interrelationship between transactive response DNA-binding protein 43 (TDP-43) and amyloid pathological processes. In some cases, however, TDP-43 lesions were detected in absence of Alzheimer pathology [53, 54]. Amnestic symptoms misleading to a

clinical diagnosis of AD might be related to hippocampal sclerosis detected in a proportion of *C9orf72* patients [53, 55].

Relation Between *C9orf72* Expansion and Non-amyotrophic Lateral Sclerosis Motor Diseases

Following the discovery of *C9orf72*, the clinical significance of its expansion in Parkinson's disease (PD), atypical parkinsonian syndromes, and other movement disorders has been debated.

Some studies initially suggested an excess of parkinsonian symptoms, PD, or atypical parkinsonism in FTD/ALS families who carry the *C9orf72* expansion [10, 21, 56–58]. However, the connections between the *C9orf72* expansion and PD, parkinsonism and other movement disorders have not been further clarified in the literature and its role beyond the FTD/ALS spectrum is still uncertain [59]. A prevalence of *C9orf72* expansion close to 1% was found in the first two investigations of large European and North American PD populations [47, 60]. However, all other cohort studies failed to replicate any association [61–65], and the frequency of *C9orf72* expansion appeared to be similar between PD patients and controls from two large meta-analyses [66, 67].

Rare *C9orf72* cases presenting with atypical parkinsonism have been described also suggesting a shared predisposition. However, further investigations in large populations of patients with multiple system atrophy (MSA) syndrome [65, 68–70], progressive supranuclear palsy (PSP) [16, 70], corticobasal syndrome (CBS) [60, 68, 70], Lewy body dementia [60], and essential tremor [61] showed that *C9orf72* has little or no contribution to the abovementioned movement disorders. Together, all these findings evidence that large repeat expansions do not play a major role in the pathogenesis of PD and related disorders, and that *C9orf72* testing should not be widely offered to these patients, but only to those who have overt symptoms and/or family history of FTD/ALS.

The implication of *C9orf72* in other movement disorders has also been investigated. *C9orf72* expansion appears to be responsible for 1–2% of patients with chorea or with Huntington-like phenocopies that are negative for *IT15* expansion [71–73]. Anecdotal cases of patients with isolated or complex cerebellar ataxia carrying *C9orf72* expansion were described [68, 74–76]. However, no association was evidenced in cerebellar ataxia study cohorts, thus suggesting that this association might be exceptional or even coincidental [77, 78].

Intermediate Alleles in Clinical Practice: A Genetic Risk Factor for Neurodegenerative Diseases?

Besides the pathogenic effect of large repeat expansion (> 100 GGGGCC), the role of intermediate alleles (20–30 GGGGCC) in neurodegenerative diseases is uncertain and their significance is still debated. In ALS, a meta-analysis provided evidence of an association of 24–30 repeat alleles with the disease, suggesting that these alleles should be considered as pathogenic [79].

Many cases with PD or parkinsonian phenotypes carrying intermediate repeats were reported [60, 66], therefore, also questioning the role of these alleles as a susceptibility factor for PD. However, associations were not systematically found in autopsy-confirmed cohorts, and meta-analyses detected a potential but low effect of intermediate repeats (10 repeats or larger) in PD susceptibility [47]. Similarly, a lack or a low association of intermediate alleles with MSA, PSP, and essential tremor likely supports that variations in *C9orf72* gene do not play a major role in the susceptibility to these diseases [63, 70]. Intermediate expansions in *C9orf72* also seem to weakly contribute to AD and dementia with Lewy bodies [47, 52, 80]. Results in CBS were more debatable, with controversial conclusions [70].

Anticipation Phenomenon: A Still Debated Question

The clinical heterogeneity of *C9orf72* is additionally characterized by an important variability in the age at onset (AO), ranging from the third decade of life to a nearly incomplete penetrance in elderly carriers [12]. As for other expansion diseases, the question of an association between expansion size and AO is raised. A clinical anticipation in *C9orf72* carriers, characterized by an earlier and more severe phenotype linked to increasing repeat number over successive generations, is also an important issue in clinical practice. There is no clear evidence for intergenerational anticipation in *C9orf72* families so far. Studies evaluating the correlation between AO and expansion size have provided conflicting results [81, 82]. Several reasons explain the difficulty in identifying these factors and precluding definite conclusions. Most studies have analyzed a correlation between AO and *C9orf72* expansion sizes in blood, but age at sampling appears as a major confounding factor [83, 84]. Additionally, the number of GGGGCC repeats in peripheral lymphocytes appears to unpredictably vary over time in subjects with multiple blood samples, as well as through generations in parents-offspring pairs [83, 84]. Finally, as in other expansion diseases, *C9orf72* expansions are unstable across tissues, producing somatic mosaicism [81]. The size variations among different tissues and the level of imprecision of Southern blot in determining the expansion size are also strong limitations to translate the observations from blood to brain tissue. Other factors such as *TMEM106B* gene and *C6orf10* locus may influence AO and survival time in *C9orf72* patients but need replications as well [85–88].

The identification of factors explaining the emergence of FTD or ALS phenotypes in *C9orf72* carriers is also a major issue. The repeat size, detected in blood, frontal cortex, cerebellum, or the spinal cord, does not appear to be associated to the clinical FTD or ALS phenotypes in any case [81]. The size of the expansion itself therefore does not seem to contribute significantly to the phenotypic variability. Intermediate alleles of the *ataxin-2 gene* (*ATXN2*) constitute a known risk factor for ALS in non-genetic populations, and several studies have evidenced that they could also drive the phenotype toward ALS in *C9orf72* patients [86, 87]. So far, our knowledge in this domain is largely incomplete, and the identification of the modifiers driving the phenotype to FTD or ALS remains a major research challenge.

Conclusions and Perspectives

Knowledge on genetic diseases, their associated phenotypes, and parameters such as penetrance and expressivity is indispensable to offer appropriate genetic diagnosis to the patients and genetic counseling to their families. In the last years, a major breakthrough has been achieved in the understanding of the genetics and molecular biology of FTD and ALS with the fast development of next generation sequencing (NGS). It is nowadays possible to analyze most genes by NGS, except *C9orf72* gene, whose expansion should be looked for separately with repeat primed polymerase chain reaction (PCR) or Southern blot. However, the interpretation of the huge load of data and the considerable number of variants of uncertain significance (VUS) generated by NGS now represent new challenges for geneticists and clinicians. Caution must be taken when interpreting uncertain results, and a good expertise in the genotypes underlying clinical phenotypes is needed.

A higher level of complexity comes from the identification of double mutations in rare patients [89]. Notably, in rare *C9orf72* carriers, an additional pathogenic mutation in another *FTD/ALS* gene have been identified [55, 90, 91]. This questions about the frequency of the coincidental occurrence of two mutations in FTD/ALS patients. It also suggests that a second mutational hit could contribute to the disease penetrance or influence the phenotypic presentation. Therefore, an extensive analysis of all known *FTD/ALS* genes may be recommended in *C9orf72* carriers, as in patients with other *FTD/ALS* gene mutations.

Although important advances have been made in *C9orf72* disease, many unsolved questions also remain a source of difficulties for family counseling. For example, the pathogenic threshold conferring a risk for FTD or ALS is not firmly established, the factors contributing to age and phenotype variability have not been clearly identified, and there is still a lack of precise information about age-related penetrance.

Important advances in our knowledge of *C9orf72*-mediated disease and its underlying pathogenesis have paved the way to new therapeutic perspectives. It is noteworthy that we are now reaching a turning point as regards the development of potentially preventive therapies. The study of presymptomatic stage in mutation carriers is currently of outmost importance, as it represents the optimal time window to test therapeutic molecules. There is a need to better clarify the definition of the presymptomatic and prodromal stages of the disease and to establish firm criteria for phenoconversion. These are new clinical challenges that, once completed, will hopefully expand the scope of potentially modifying therapies targeting the earliest disease stage in genetic FTD.

Conflict of Interest The authors declare no conflicts of interest.

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Clinical and Neuroimaging Aspects of Familial Frontotemporal Lobar Degeneration Associated with *MAPT* and *GRN* Mutations

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Abbreviations

ALS	amyotrophic lateral sclerosis
bvFTD	behavioral variant frontotemporal dementia
c9FTD/ALS	frontotemporal dementia and/or amyotrophic lateral sclerosis linked to chromosome 9
C9orf72	gene encoding *chromosome 9 open reading frame 72*
CBS	corticobasal syndrome
CNS	central nervous system
FDG-PET	fluorodeoxyglucose positron emission tomography
FTD	frontotemporal dementia
FTD/ALS	frontotemporal dementia with amyotrophic lateral sclerosis
FTLD	frontotemporal lobar degeneration
GRN	gene encoding progranulin (or granulin)
MAPT	gene encoding microtubule-associated protein tau
MRI	magnetic resonance imaging
PPA	primary progressive aphasia

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Introduction

Frontotemporal lobar degeneration (FTLD) is an overarching term for a group of neurodegenerative disorders that are typically associated with progressive degeneration in the frontal and anterior temporal lobes [1]. FTLD can involve many structures in the central nervous system (CNS), and therefore can present with a wide variety of symptoms, including the behavioral variant of frontotemporal dementia (bvFTD), the nonfluent and semantic variants of primary progressive aphasia (nfvPPA and svPPA), progressive supranuclear palsy syndrome (PSP), corticobasal syndrome (CBS), and amyotrophic lateral sclerosis, with or without other features of frontotemporal disease (ALS and FTD/ALS) [2]. In about 20% of people, FTLD is caused by genetic mutations, and therefore affects multiple members within the same family (familial frontotemporal lobar degeneration [f-FTLD]). F-FTLD has been associated with mutations in a number of genes, including the genes encoding microtubule-associated protein tau *(MAPT)*, progranulin *(GRN)*, chromosome 9 open reading frame 72 gene *(C9orf72),* and less commonly valosin-containing protein *(VCP)*, TAR DNA-binding protein *(TARDBP)*, and fused in sarcoma *(FUS)*, among others. The clinical and imaging findings associated with the mutation in *C9orf72* are described in a separate chapter, and this chapter will focus on those findings in *MAPT* and *GRN*.

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Historical Perspectives

The search for causative genes in f-FTLD was initiated with the identification of linkage between the symptoms of FTLD and a locus on the q21–22 region of chromosome 17 [3]. This finding prompted the first conference devoted to this topic in Ann Arbor, Michigan, in 1996, which focused on the clinical, pathological, and genetic features of frontotemporal dementia with parkinsonism (FTDP) linked to chromosome 17, which had been identified in a number of families up until then [4]. Researchers who characterized these early families noted that, despite common themes of disinhibition and parkinsonism across these kindreds, there was still considerable clinical heterogeneity within and across families [3, 4]. Beyond their implications for our understanding of the causes and pathogenesis of FTLD, these descriptions highlighted an important aspect of FTLD, which is that the same pathological mechanism can be associated with a variety of clinical manifestations. This observation has continued to be reinforced as a core clinical feature as knowledge about f-FTLD has expanded. As discussed below, this represents a challenge for diagnosis and clinical trials in FTLD and presents a fascinating biological mystery regarding the mechanisms by which the same molecular mechanism can be manifest by dysfunction in different neurological systems across people. In addition, the variation in clinical features across families prompted speculation that there might be another locus on chromosome 17 that accounts for disease in some families.

Soon after the link to chromosome 17 was discovered, mutations in *MAPT* were identified [5]. Even after the discovery that FTLD could be caused by mutations in *MAPT*, it was noted that a significant minority of patients with FTDP linked to chromosome 17 had no identifiable mutations in *MAPT*, nor did they have any tau-positive inclusions at autopsy [6]. This mystery was solved when it was discovered that mutations in *GRN*, which is also on chromosome 17, could also be associated with f-FTLD [7, 8], accounting for FTLD in all of these remaining chromosome 17-linked families. Subsequently, many other kindreds carrying mutations in *GRN* have been reported, thereby solving a decade-long conundrum and providing a remarkable insight into genetic diversity. The *GRN* gene is only 1.7 Mb centromeric to *MAPT* on chromosome 17, demonstrating that two apparently different genes reside very close to each other on the same chromosome and cause a similar phenotype.

This chapter summarizes the demographic/inheritance characteristics, histopathology, pathophysiology, key clinical aspects, and neuroimaging findings of disease due to *MAPT* and *GRN* mutations using data and findings from prior reports that included large numbers of informative cases and kindreds, in particular some recent publications that have provided extensive data [9–12]. While the features of FTLD due to *GRN* and *MAPT* mutations show many similarities, there are also unique features associated with mutations in each of these genes. These features are discussed in more detail below, and some of them are summarized in Table 1.

Demographic and Inheritance Characteristics

There are currently 67 known mutations in *MAPT* and 130 in *GRN* [9]. Additionally, there are over 790 affected individuals among at least 250 kindreds with mutations in *MAPT,* and over 1170 affected individuals among at least 480 kindreds with mutations in *GRN* [9]. The vast majority of what is known about f-FTLD comes from kindreds identified in the United States and Europe [9, 13], and thus, inferences about the relative prevalence of FTLD mutations across races and ethnicities is largely unknown. That said, studies in China, Korea, and Japan have identified mutations in the *MAPT* and *GRN* genes, as well as *C9orf72* and other genes [14–19]. Case reports describing *MAPT* and *GRN* mutations in people of African descent [20, 21] and *GRN* mutations in Latinos [22] have also been published.

The male-to-female ratio for mutations in both genes is close to 1:1, although recent studies have suggested a slight predilection for females in *GRN* [9]. The mean age of onset is around

Table 1 Comparisons between key characteristics associated with mutations in microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*)

	MAPT	*GRN*
Known number of distinct mutations[a]	67	130
Known number of affected individuals[a]	>790	>1170
Known number of kindreds[a]	250	480
Mode of inheritance	Autosomal dominant	Autosomal dominant
Penetrance	>95%	90% by age 70
Sex[a]	F 51%/M 49%	F 58%/M 42%
Onset age – mean (years)[a]	50	61
Onset age – range (years)[a]	17–82	25–90
Duration of illness – mean (years)[a]	9	7
Duration of illness – range (years)[a]	0–45	0–27
Cognitive features		
Executive dysfunction	++++	++++
Language impairment	+++	++++
Memory impairment	++	++
Visuospatial impairment	+	++
Behavioral features		
Personality/behavior changes	++++	++++
Psychotic features	+	+
Motor features		
Limb apraxia	+	+ – +++
Parkinsonism	++	+++
Motor neuron disease	+	+
Clinical syndromes		
Behavioral variant FTD	++++	++++
Nonfluent variant PPA	+	+++
Semantic variant PPA	+	+
Logopenic variant PPA	0	+
Amnestic mild cognitive impairment	+	+
Alzheimer's type dementia	+	++
Corticobasal syndrome	+	++
Posterior cortical atrophy	0	+
Parkinson's disease	+	+
Progressive supranuclear palsy	+	0
Parkinson's disease + dementia	+	+
Dementia with Lewy bodies	+	+
Amyotrophic lateral sclerosis	+	+
MRI and FDG-PET findings		
Frontal abnormalities	+++	++++
Temporal abnormalities	++++	+++
Parietal abnormalities	+	++
Occipital abnormalities	0	0
Parenchymal signal changes on MRI	+	++
Symmetry vs. asymmetry	Usually symmetric	Often asymmetric

++++ = very frequently reported, +++ = frequently reported, ++ infrequently reported, + = rare, 0 = no definite cases reported to date

AD autosomal dominant, *F* female, *FDG-PET* fluorodeoxyglucose positron emission tomography, *f-FTLD* familial frontotemporal lobar degeneration, *FTD* frontotemporal dementia, *M* male, *MRI* magnetic resonance imaging, *PPA* primary progressive aphasia

[a]data from Moore et al. Lancet Neurol 2019

50 years for *MAPT* and around 61 years for *GRN*, with a wide range in age of onset in both mutations (17–82 years for *MAPT* and 25–90 years for *GRN*) [9]. Duration of clinical symptoms also varies widely, with *MAPT* being 0–45 years and *GRN* being 0–27 years [9].

F-FTLD associated with mutations in both *MAPT* and *GRN* is inherited in an autosomal dominant fashion. Penetrance is high but not complete, with penetrance appearing to be greater in *MAPT* than *GRN* [9, 11]. Seemingly "sporadic" cases have been identified in both genetic

cohorts [9, 11]; some of these appear to be de novo mutations, while some have been found to reflect more convincing germline mosaics [23]. Anticipation has not been strongly suggested, but there is evidence that a slightly lower age of onset can occur in successive generations in both genes [9]. This may be explained by presentation bias, such that symptoms may be recognized earlier in individuals in successive generations due to their family history.

In contrast to familial Alzheimer's disease, where estimating the age of onset among asymptomatic mutation carriers based on parental and other relatives' age of onset is relatively reliable [24, 25], the predictability in *MAPT* and particularly *GRN* kindreds is more challenging [9]. Ongoing natural history studies such as the ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD; https://www.allftd.org/) consortium in North America [26], the Genetic Frontotemporal Dementia Initiative (GENFI; http://genfi.org.uk/) consortium in Europe, the Dominantly Inherited Non-Alzheimer's Disease (DINAD) study in Australia, and recently formed Frontotemporal Dementia Prevention Initiative (FPI; http://genfi.org.uk/fpi.html) consortium involving global consortia are seeking to improve this predictability by combining clinical and biomarker data to generate predictive models to facilitate current and future clinical trials involving potential disease-modifying therapies [12, 27].

Histopathology and Pathophysiology

Frontotemporal lobar degeneration is thought to be caused most commonly by the accumulation of one of two proteins in CNS tissue: microtubule-associated protein tau, or transactive response DNA binding protein molecular weight 43 (abbreviated TDP), each of which is thought to account for roughly half of FTLD cases. *MAPT* and *GRN* mutations represent genetic causes for each of these two common FTLD-associated protein disorders. In the case of *MAPT*, autopsy studies demonstrate aggregation of microtubule-associated tau protein in paired helical filaments and neurofibrillary tangles in CNS tissue [28]. The tau protein plays an important role in the stabilization of microtubules and therefore in maintenance of the neuronal cytoskeleton that maintains neuronal structure and intraneuronal transport, among other functions [29, 30]. Although the precise mechanisms by which *MAPT* mutations cause cellular injury are not known, the mutations clearly have effects on tau function, with the specific effect depending on the precise mutation, and these differing effects can be associated with specific features of tau protein aggregation. Most *MAPT* mutations affect the region on the gene that encodes the microtubule-binding portion of the protein. They can be classified as missense mutations, which alter the sequence of the protein and usually influence the affinity of tau for microtubules, or splicing mutations, which influence the isoform of tau that is produced, favoring a form that contains either three or four repetitions of the carboxy-terminal sequence that is encoded by exon 10 of the gene, called 3-repeat (3R) or 4-repeat (4R) tau. In the absence of *MAPT* mutations, most cells contain the 3R and 4R isoforms of tau in roughly equal proportions, and this is also true in many *MAPT* mutations [29, 30]. Depending on how the mutation affects the protein and the post-translational modifications, tau protein aggregates can be found predominantly in the neurons, or in both glia and neurons. Furthermore, the features of the tau inclusions can vary and take on a wide variety of characteristics, including aggregation in inclusions similar to Pick bodies, as can be seen with the G389R mutations, or neurofibrillary tangles that are very similar to those seen in Alzheimer's disease, as can be seen with the V337M and R406W mutations [31]. Recent work has also highlighted the fact that abnormal tau proteins can induce other tau proteins to take on a pathological confirmation in a prion-like fashion [29, 30], and this has been proposed as a mechanism by which tau-mediated neurodegenerative disease spreads through neural systems [32].

In contrast to *MAPT*, *GRN* mutations are invariably associated with accumulation of TDP

pathology [33], specifically in the form of TDP type A pathology, which is characterized by lentiform neuronal aggregates of TDP [34]. The mechanisms by which *GRN* mutations cause accumulation of TDP and neurodegeneration are incompletely understood. The primary effect of all *GRN* mutations is reduction in the production of the progranulin (PGRN) protein [35]. PGRN is normally broken into cleavage products called granulins, and PGRN and various granulin proteins have been shown to regulate survival and morphology of neurons, with PGRN promoting neuronal growth and various granulin proteins having different effects on neurons [35]. Beyond its effects on neuronal growth, PGRN also has important roles in the inflammatory response and in lysosomal function [35–37]. Thus, there are at least three major biological pathways through which PGRN deficiency may lead to disease, but which of these is most important, or whether disease results from a combination of these effects, is not yet known. The available knowledge on PGRN biology and its potential relationship to FTLD is extensively reviewed in another chapter in this book.

Cognitive and Behavioral Features

Mutations that cause FTLD are associated with a wide variety of clinical symptoms, and patients often present with one of the syndromes that are seen in sporadic FTLD, but some types of symptoms are seen more commonly in f-FTLD compared with sporadic FTLD. The bvFTD syndrome, characterized by early socioemotional changes that include disinhibition, apathy, loss of sympathy and empathy, stereotyped or compulsive/ritualistic behavior, and dietary changes, with or without early executive dysfunction, and usually sparing memory and visuospatial function [38–40], is the most common presentation with both mutations, occurring in about 40% of carriers [9]. These clinical changes are accompanied by atrophy and hypometabolism in orbitofrontal cortex and anterior cingulate cortex, along with dorsolateral prefrontal cortex – a pattern typical of bvFTD. Both the clinical and imaging abnormalities in bvFTD due to mutations are very similar to the features that characterize sporadic bvFTD [41–46].

Language impairment is also relatively common in both mutation groups, but the qualitative aspects tend to be different. In *MAPT* mutation carriers, the topography of degeneration usually begins in the medial and anterior temporal lobes, leading to loss of semantic knowledge that begins with word and proper name retrieval problems and progresses to more generalized loss of knowledge about words and objects (svPPA; [47]). Loss of semantic knowledge can also affect knowledge about people (e.g., family members) and previously familiar locations [48, 43–46, 49]. Affected patients or their family members may state that they have "memory problems" when in fact they are describing problems recalling the names of people or objects rather than problems remembering recent events (episodic memory). Over time, verbal and semantic fluency become impaired as more frontal and posterior temporal language networks become affected.

In *GRN* mutation carriers, the topography of degeneration tends to be far more focal and asymmetric, often with disproportionate involvement of either the left or the right hemisphere [45, 46, 50]. If the anterior temporal lobe of the dominant hemisphere is the initial focus of degeneration, a semantic naming problem is prominent, similar to what is described above for *MAPT*; if the anterior temporal lobe of the nondominant hemisphere is affected, early semantic aphasia as well as object agnosia/prosopagnosia are the major manifestations. A nonfluent/agrammatic aphasia syndrome can occur in *GRN* mutation carriers (nfvPPA), with degeneration being prominent around Broca's area and the adjacent supplementary motor area of the dominant hemisphere [50, 51].

While the most common cognitive and behavioral features in both *MAPT* and *GRN* mutations are similar to those seen in sporadic FTLD, several other clinical syndromes can be seen with these mutations that are not typically associated with FTLD. A prominent amnestic syndrome (i.e., amnestic mild cognitive impairment, or memory-predominant dementia syndrome) can

occur in both genetic groups, which has led to many such individuals being diagnosed with clinically suspected Alzheimer's disease (AD) [52].

Focal/asymmetric cortical degeneration syndromes similar to those seen in AD can also occur and are far more common in *GRN* than *MAPT* mutations. For instance, while *GRN* mutations can be associated with nfvPPA and svPPA, both of which are typical of FTLD, degeneration in the posterior perirolandic region of the dominant hemisphere can also occur with *GRN* mutations, leading to a logopenic primary progressive aphasia syndrome (lvPPA), which is characterized by word retrieval problems but without semantic loss, and progresses to empty, poorly directed speech. When this syndrome occurs outside of the setting of mutations, it is usually due to AD pathology [47]. Posterior degeneration in the right-greater-than-left hemisphere can also occur with *GRN* mutations, resulting in prominent visuospatial impairment, optic ataxia, ocular apraxia, simultanagnosia, dressing apraxia, spatial disorientation, and/or hemineglect: these are the typical elements of the posterior cortical atrophy syndrome (PCA; [51, 53]) which is also often due to AD pathology when it occurs outside of the setting of mutations [54, 55]. Visuospatial presentations are rare with *MAPT* mutations. Corticobasal syndrome (CBS) is a syndrome of unilateral or asymmetric limb apraxia and limb rigidity, which can also include other features such alien limb phenomenon, myoclonus, dystonia, etc. [56]. CBS can occur with either *MAPT* or *GRN* mutations [50, 51]. While this syndrome is typically associated with FTLD, it is also commonly caused by AD [57], and so a patient presenting with this syndrome without a known genetic mutation or strong family history of FTLD may be mistaken as a case of AD.

Lastly, more bizarre behavioral manifestations that are not core features of sporadic FTLD, including bizarre, schizophrenia-like delusions, visual or auditory hallucinations, and manic symptomatology, can occur with FTLD mutations. These features appear to be most common in *C9orf72* mutation carriers [58, 59], but they can occur in *MAPT* and *GRN* carriers as well, leading to erroneous diagnoses of schizophrenia, bipolar disorder, or other psychiatric illnesses [3, 22, 60, 61].

Motor Features

While the documentation of other clinical features has varied across reports, many cases develop parkinsonism as the course progresses in both *MAPT* and *GRN* carriers [51, 62, 63]. Among *MAPT* mutation carriers, bradykinesia, rigidity, and postural instability are most common, with a few patients having a tremor-predominant syndrome [64, 65]. All of these features can lead to patients being diagnosed with Parkinson's disease or dementia with Lewy bodies. Many develop a PSP/Richardson's syndrome-like phenotype in the more advanced stage of the disorder [65]. Limb apraxia is very rarely documented in *MAPT* [66], but can occur in *GRN* mutation carriers, particularly when the parietal lobe is affected [50, 51]. Other features such as alien limb syndrome, myoclonus, dystonia, etc. also occur in *GRN* mutation carriers [50, 51]. Upper and/or lower motor neuron dysfunction suggestive of ALS is rare in both groups.

Variation Within and Across Families and Mutation-Specific Syndromes

One of the most striking features of FTLD due to genetic mutations is the clinical heterogeneity. As reviewed above, patients can present with any of the FTLD syndromes, in addition to the typical and atypical syndromes associated with AD pathology. While there is some association between the type of mutation, the family history, and the clinical presentation, the ability to predict the clinical syndrome that will emerge in an individual based on these factors is limited. *MAPT* mutations tend to have more similarity within families compared with *GRN* mutations. The clinical phenotype among affected relatives in the same *MAPT* kindred tend to be relatively similar (with some notable exceptions). In addition, recent work has shown that age of symptom onset

for an individual within a *MAPT* family is significantly correlated with the age of onset in their parents and other relatives [9]. There is evidence that some of the clinical symptomatology in *MAPT* mutations can be accounted for by the specific type of mutations (see Table 2). For example, mutations that are associated with accumulation of AD-like tau inclusions (e.g., V337M and R406W) are more likely to present with amnestic symptoms similar to AD, and some mutations, such as the N279K and IVS10 + 16 > T, have a particularly strong association with parkinsonism. Age of onset is also somewhat predicted by mutation, with some mutations such as the L266V, G335S, and G335V being associated with ages of onset lower than 30. A recent analysis confirmed that mutation type explained a significant amount of variation in age of onset, in addition to familial age of onset [9]. That said, ages of onset and clinical phenotypes across individuals can still be quite variable within kindreds, and families with individual ages of onset as disparate as 60 years apart have been reported. Some of the most common mutations, including the P301L and N279K, are associated with significant variability in clinical phenotype and age of onset. The reason for the significant genetic variability even within families is not known. Genetic background is certainly one possible mechanism, but no genetic modifiers that influence phenotype or age of onset have been identified in *MAPT*-associated disease. Such an analysis would have a low power to detect modifier effects because of the relatively small number of known symptomatic carriers.

Phenotypic variability within *GRN* families is very common [10, 50, 51]. Some reports have linked specific *GRN* mutations to specific phenotypes (Table 2). For instance, the IVS1 + 5G > C mutation is commonly associated with nfvPPA, while the T52fs and T272fs mutations often present with an AD-like phenotype [51]. The Q300X and IVS7-2A > G mutations have been associated with an ALS phenotype [9]. Despite these associations, the clinical presentations within *GRN* mutation families are quite variable, and a given family can certainly include one person

Table 2 Notable features associated with specific mutations in genes encoding microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*)

MAPT	
L266V	Many have a very early age of onset (age < 30)
N279K	Parkinsonism early in the course; phenotype can be classic PD syndrome with rest tremor at least partially responsive to levodopa therapy. One of the more common mutations in *MAPT*
P301L	Most common mutation in *MAPT* (>230 known individuals). A minority have a very early age of onset (age < 30)
IVS10 + 3G > A	Highly variable age of onset; minority have a very early age of onset (age < 30)
IVS10 + 16C > T	One of the more common mutations in *MAPT* (>140 known individuals); a PD-predominant syndrome occurs in a minority
G335S, G335V	Most have very young onset (age < 30), can be rapidly progressive
Q336H	While this mutation is very rare, the FTD/ALS phenotype has occurred in multiple affected individuals
V337M	Often prominent amnestic component early in the course, and an AD-like phenotype can occur; can be very slow rate of progression
G389R	Very young onset, rapidly progressive. Pathology shows Pick bodies
R406W	Often prominent amnestic component early in the course, and an AD-like phenotype is common; can be very slow rate of progression
GRN	
IVS1 + 5G > C	Nonfluent variant PPA is the predominant phenotype
T52fs	An AD-like phenotype is common
T272fs	The most common mutation in *GRN* (>200 known individuals); an AD-like phenotype is common

(continued)

Table 2 (continued)

R493X	One of the more common mutations in *GRN* (>55 known individuals); an AD-like phenotype is common
Q300X	One of the few *GRN* mutations associated with ALS phenotype
IVS7-2A > G	One of the few *GRN* mutations associated with ALS phenotype
A472fs	While this mutation is very rare, the semantic variant PPA phenotype has occurred in multiple affected individuals

AD Alzheimer's disease, *ALS* amyotrophic lateral sclerosis, *FTD/ALS* combined frontotemporal dementia and amyotrophic lateral sclerosis, *PD* Parkinson's disease, *PPA* primary progressive aphasia

with bvFTD, another with a PPA, and a third with an AD-like presentation. In addition, individual age of onset varies considerably in *GRN* families and is much less predictable based on parental and familial age of onset compared with *MAPT* families [9]. Similarly, the specific type of *GRN* mutation does not strongly predict age of onset or disease duration [9]. Because of this variability and the stronger association of *GRN* mutations with AD-like clinical presentations, family histories in these families can potentially be interpreted as suggesting familial AD. Alternatively, the family history can be characterized by different individuals having apparently different diseases, so that the family and the clinician may not initially suspect that a single mutation is affecting the family. The variation across individuals carrying *GRN* mutations is particularly remarkable, given that the vast majority of mutations have the same primary effect on biology, which is a roughly 50% reduction in production of the PGRN protein. Again, genetic background has been considered as a potential explanation, and variation in the *TMEM106B* and *GFRA2* genes has been identified as conferring some protection, but no clear genetic modifiers that associate with age of onset or phenotypic presentation have been identified [67, 68].

The variation in age of onset and phenotype is a significant impediment in developing treatments for disease due to *MAPT* and *GRN* mutations. One reason is that studies focusing on symptomatic carriers will face obstacles in developing outcome measures suitable for participants with changes in social-emotional function as well as patients with language dysfunction and amnesia who would all be in the same study [27]. In addition, one goal for intervention studies would be to begin treatment before the onset of symptoms in order to demonstrate delay or prevention of symptoms. Such studies would have to focus on individuals who are most likely to develop symptoms within 1 to 2 years, the duration of a typical study. The significant variability in age of onset, along with the variation in early symptoms, makes it very difficult to identify such patients. The large studies referred to above are all seeking to develop better methods for studying participants with FTLD-causing mutations in clinical trials [12].

Neuroimaging and Other Biological Markers

The neuroimaging features in *MAPT* versus *GRN* mutation carriers are quite different, and the patterns of regional topography can provide clues to the presence of a mutation when combined with the clinical phenotype and family history.

As noted above, the evolution of degeneration in *MAPT* mutation carriers tends to begin with symmetric involvement of the bilateral medial and anterior temporal lobes with eventual involvement of the bilateral frontotemporal neural networks [10, 12, 45, 46, 69]. This topography underlies the semantic loss, object agnosia, and other cognitive and behavioral manifestations. Hippocampal atrophy is the most common feature in *MAPT* mutation carriers [10, 70], thereby explaining prominent memory impairment when this is present. Since the parietal and occipital lobes are relatively spared, these regions appear preserved on MRI and FDG-PET scans.

While clinical syndromes associated with symmetric changes on MRI and FDG-PET scans can occur in *GRN* mutation carriers, focal, asymmetric atrophy and hypometabolism early in the course are far more common, with the focality or asymmetry persisting over the course of the dis-

order [45, 46, 69, 71, 72]. As one would expect, the topography of atrophy or hypometabolism correlates with the clinical syndrome (e.g., left hemisphere disease being associated with language disorders, right hemisphere disease with visuospatial dysfunction). Furthermore, the tendency for imaging abnormalities to "respect the midline" in *GRN* mutation carriers is striking, with no atrophy/hypometabolism in one cerebral hemisphere despite profound abnormalities in the affected hemisphere. Other neuroimaging modalities, such as MRI-based diffusion-weighting imaging, magnetic resonance spectroscopy, etc., and longitudinal studies provide additional insights on f-FTLD [12, 73–79]. Representative MRI and FDG-PET scans from affected individuals are shown in Fig. 1.

Recent work has sought to identify additional biological markers in these disorders. The development of PET ligands that bind tau protein in AD [80] led to studies examining the utility of these agents in FTLD. While these studies have indicated increased uptake in patients with *MAPT* mutations that cause AD-like inclusions, other types of *MAPT* mutations unfortunately do not show increased binding [81, 82]. Furthermore, uptake can also be seen in *GRN* and *C9orf72* mutations, indicating that non-specific binding occurs with currently available tau PET ligands, severely limiting their utility.

Fluid biomarkers are also a major focus for development. In *GRN* carriers, genetic haploinsufficiency results in reduced production of PGRN messenger RNA and protein, which can be quantified in the CSF or blood [83, 84]. These reduced levels are present throughout life in carriers and have no relationship with any clinical features and therefore have no utility for tracking the natural history of disease or prognosis [85]. However, increases in PGRN levels in the setting of drug trials may indicate significant biological effects of a potential treatment and may predict clinical response. No fluid biomarkers that track tau concentrations in *MAPT* carriers have yet been developed.

Neurofilament light chain (NfL) is a neuronal cytoskeletal protein that is elevated in symptomatic FTLD and other neurodegenerative diseases [86]. While not specific to any particular mutation or form of FTLD, higher levels of CSF and blood NfL are associated with greater degrees of atrophy and clinical impairment, both cross-sectionally and longitudinally, indicating that NfL is an indicator of the intensity of neurodegeneration [87, 88]. Recent work has shown that NfL levels predict increased rates of decline and shorter survival in f-FTLD mutation carriers, including *MAPT* and *GRN* mutations [89]. Furthermore, higher levels of NfL and rises in NfL over time are associated with development of symptoms in asymptomatic carriers [90].

A recent study also showed that plasma glial fibrillary acidic protein (GFAP) is elevated in symptomatic *GRN*, but not *MAPT* carriers, and that increased GFAP levels are associated with lower cognitive scores and brain volumes in asymptomatic *GRN* mutation carriers [91]. Measures of immune activation, including sCD163, CCL18, LBP, sCD14, IL-18, and CRP, correlate with severity of clinical symptoms and brain atrophy in *GRN*-associated disease [92]. All of these markers may provide useful indicators of emerging disease and also allow tracking of therapeutic effects in drug trials.

Prediction of Symptom Onset in Asymptomatic Carriers

Reliable approaches for predicting the age when symptoms will develop are important for individuals carrying these mutations to help with life planning. In addition, as noted above, prediction tools are important for selection of participants in clinical trials. Although studies have shown that abnormal performance on cognitive testing can be seen prior to frank development of symptoms in f-FTLD [43], the specific tests that show impairment vary considerably across individuals [10], even when carrying the same mutation, so that monitoring of a single or just a few tests is unlikely to provide adequate sensitivity and specificity. Several studies have indicated that reductions in brain volume precede onset of symptoms by up to 10 years in f-FTLD mutation carriers [43], and that quantification of the degree and

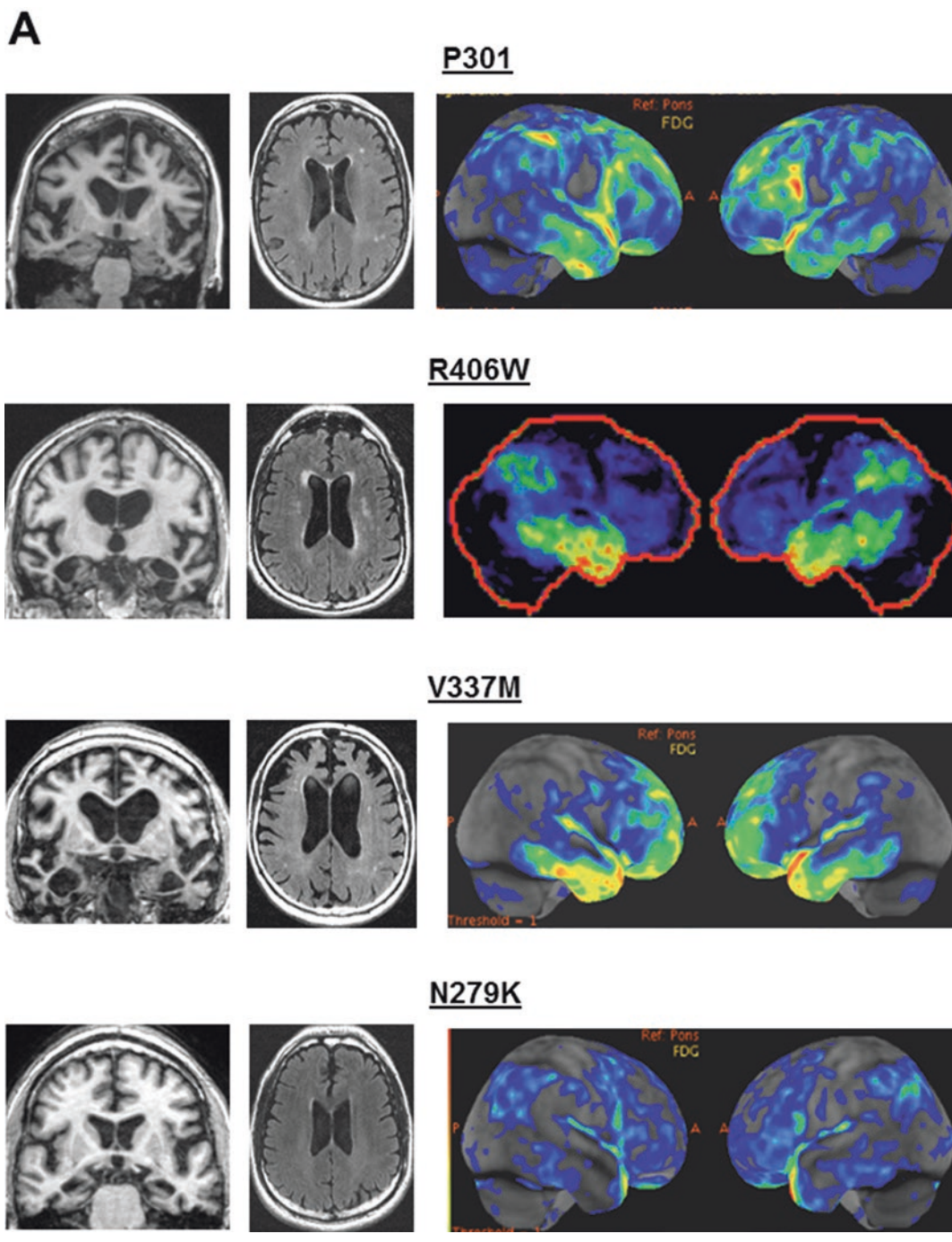

Fig. 1 Representative scans of individuals with *MAPT* (**a**) and *GRN* (**b**) mutations, showing coronal T1-weighted magnetic resonance images (far left), axial fluid attenuation inversion recovery magnetic resonance images (middle), and right and left lateral statistical map images from FDG-PET scans (right). Increasing degrees of hypometabolism on FDG-PET are represented by the following color scheme: black/gray (normal) – blue – green – yellow – orange – red (maximally abnormal). The scans in (**a**) are from symptomatic *MAPT* mutation carriers: P301L (age 53 with bvFTD features for 3 years), R406W (age 68 with early amnestic features followed by more typical yet slowly progressive bvFTD features for >20 years), V337M (age 67 with slowly progressive bvFTD features for >20 years), and N279K (age 50 with early amnestic and parkinsonian features followed by a mixed bvFTD/PSP phenotype for 3 years). Note the hippocampal atrophy in the R406W, V337, and N279K mutation cases, and frontal

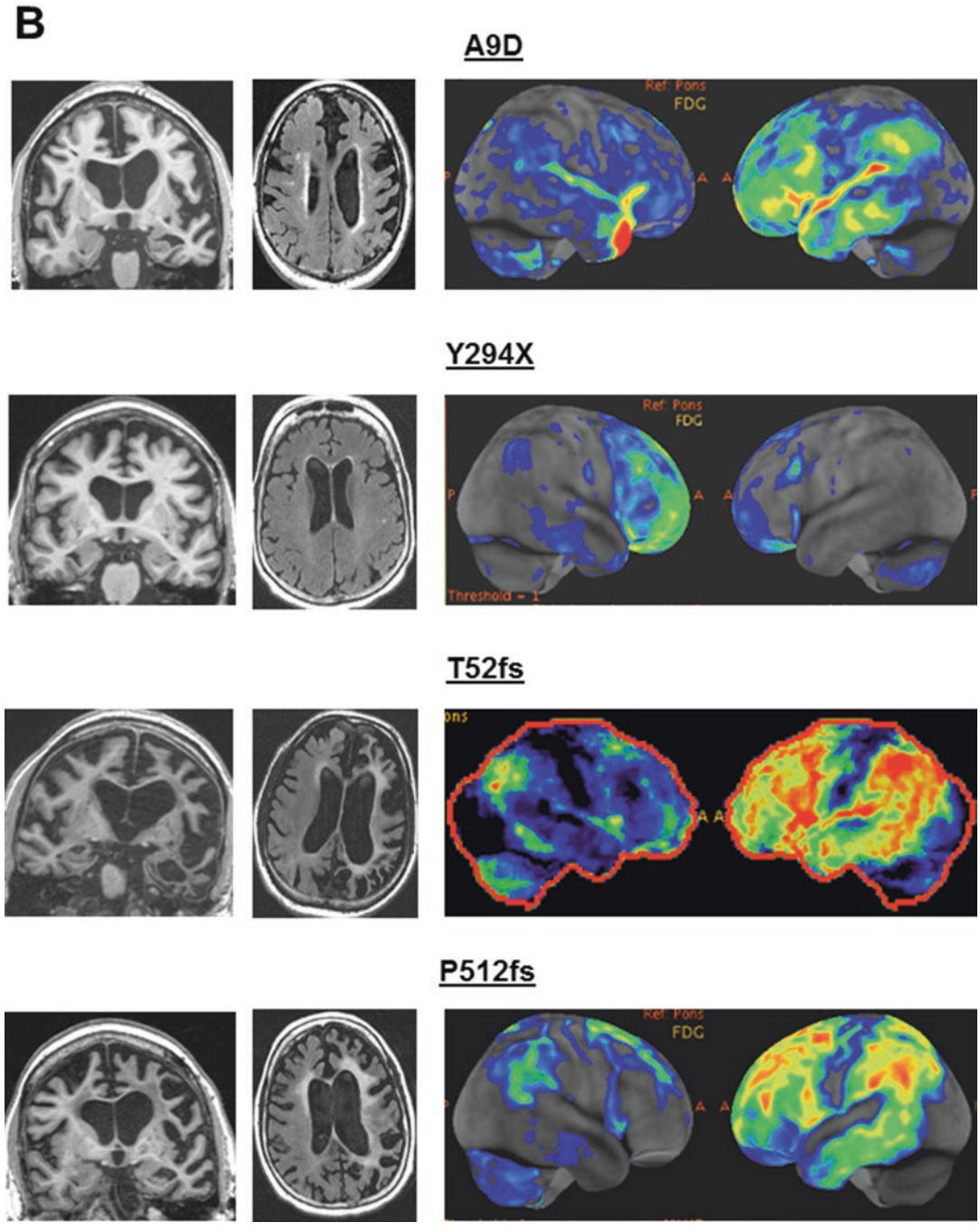

Fig 1 (Continued) and/or temporal predominant hypometabolism on the FDG-PET scans. Also note that the topographic distribution of atrophy and hypometabolism is relatively symmetric, which is typical of affected *MAPT* mutation carriers. The scans in (**b**) are from symptomatic *GRN* mutation carriers: A9D (age 72 with mixed PPA/bvFTD features for 3 years), Y294X (age 70 with bvFTD features for 3 years), T52fs (age 68 with early amnestic features followed by PPA and then CBS features evolving over an >8 year period), and P512fs (age 64 with early PPA features followed by CBS features for 2 years). Note the striking degree of asymmetry in all cases, which is typical of affected *GRN* mutation carriers. Abbreviations: bvFTD behavioral variant frontotemporal dementia, CBS corticobasal syndrome, FDG-PET fluorodeoxyglucose positron emission tomography, PPA primary progressive aphasia, PSP progressive supranuclear palsy

Table 3 Clues to suspect a mutation in microtubule-associated protein tau (*MAPT*) or progranulin (*GRN*)

MAPT
bvFTD +/− parkinsonism phenotype in the setting of a positive family history of dementia and/or parkinsonism
Very early age of onset and/or rapidly progressive course regardless of the clinical phenotype and presence/absence of a family history of dementia, parkinsonism, or ALS
Prominent memory impairment in the context of otherwise classic bvFTD clinical features
Relatively symmetric temporal and/or frontal abnormalities on MRI or FDG-PET
GRN
Any neurodegenerative syndrome in the context of a positive family history of dementia or parkinsonism – particularly if:
The patient's clinical findings and/or imaging abnormalities have focal or asymmetric features
One or more affected relatives have features or diagnoses (e.g., PPA, CBS) that suggest focal or asymmetric abnormalities

ALS amyotrophic lateral sclerosis, *bvFTD* behavioral variant frontotemporal dementia, *CBS* corticobasal syndrome, *FDG-PET* fluorodeoxyglucose positron emission tomography, *MRI* magnetic resonance imaging, *PPA* primary progressive aphasia

pattern of brain atrophy in individuals can significantly improve prediction of symptom development compared with age alone [93]. Furthermore, it has been shown that acceleration of the rates of brain volume loss and white matter degradation occurs within the few years prior to development of symptoms in *MAPT* carriers [12, 74–77]. Abnormalities in other types of imaging, such as MR spectroscopy and FLAIR, can also be seen in asymptomatic *MAPT* carriers prior to development of symptoms [78, 94]. Lastly, as noted above, rises in levels of NfL appear to predict development of symptoms. Most of these findings have been identified in relatively small groups of individuals who have been observed to convert from asymptomatic to symptomatic. Additional studies will need to be done to verify the utility of these measures, to quantify their predictive value, and to develop models based on combinations of these predictors to identify individuals close to this conversion with high sensitivity and specificity.

Clues for the Clinician to Suspect an *MAPT* or *GRN* Mutation

An important consideration for any clinician evaluating a patient for changes in cognition, behavior, or motor functioning is when to be suspicious of a mutation in *MAPT* or *GRN*. Family history is one of the most important features, and a thorough family history should be taken in any individual with an FTLD syndrome, a dementia syndrome with an age of onset younger than 65, or a rapidly progressive dementia syndrome. Any evidence of neurodegenerative disease in multiple family members, even if the syndromes differ across individuals, should raise concerns, and a mixture of motor, cognitive, and behavioral symptoms across family members is typical. It is worth noting that mutations are a much more common cause of f-FTLD than a cause of familial AD, which is only due to a mutation in a very small proportion of AD patients [95].

Another scenario that should raise concerns about a mutation would be the presence of a neurodegenerative syndrome with features of FTLD that are not entirely typical of the syndrome usually seen in sporadic cases. For instance, a patient with relatively symmetric atrophy of the anterior and medial temporal lobes and mild semantic loss mixed with amnesia of the type seen in typical AD has some features of svPPA but would be atypical because of the symmetry of temporal lobe changes and episodic memory loss. Such a patient might be an *MAPT* mutation carrier. Marked asymmetry on brain imaging is a finding that should prompt consideration of a *GRN* mutation. These clinical clues are summarized in Table 3.

Conclusions and Future Directions

F-FTLD syndromes due to mutations in the *MAPT* and *GRN* genes are important entities, because they offer many opportunities to understand the pathophysiology that leads to aggregation of tau and transactive response DNA-binding protein 43 (TDP-43), which are the two most

common proteins associated with FTLD. The variability in clinical presentation across individuals with these mutations also offers an opportunity to understand how a single biological change can be manifest in many different effects in the CNS. Carriers of these mutations are also important for clinical trials of FTLD treatments because such studies could be assured that all individuals enrolling in the study are affected by the targeted biological mechanism if they recruit mutation carriers. The natural history studies described above (i.e., ALLFTD, GENFI, DINAD, FPI, others) will expand the characterization of kindreds with f-FTLD, as academic and industry investigators continue efforts to develop therapies that may slow the rate of progression, delay the onset of symptoms, and ultimately prevent the development of symptoms among those with mutations in *MAPT* or *GRN* [12, 27].

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Neuroimaging in Frontotemporal Lobar Degeneration: Research and Clinical Utility

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Introduction

The clinical and pathological heterogeneity in frontotemporal lobar degeneration (FTLD) presents a variety of challenges to clinicians and researchers, including accurate and timely diagnosis, prognostication, monitoring, and identification of appropriate endpoints in clinical trials. Neuroimaging offers a powerful set of tools to visualize structural, functional, and pathological changes associated with FTLD. This is particularly true of the three most common clinical presentations of sporadic FTLD—behavioral variant frontotemporal dementia (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent/agrammatic variant PPA (nfvPPA)—as the neuroanatomical and hypometabolic signatures of these three syndromes are generally well defined.

In this chapter, we selectively review evidence supporting the utility of neuroimaging biomarkers in bvFTD, svPPA, and nfvPPA, with an emphasis on current and future clinical applications. We begin by discussing patterns of abnormalities and diagnostic utility among those neuroimaging methods most commonly used in clinical settings, including structural T1 and fluorodeoxyglucose positron emission tomography (FDG-PET). This is followed by a review of imaging methods used in research settings that show a promising role in clinical settings or as endpoints in clinical trials.

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Imaging Modalities Commonly Used in Clinical Settings

Consensus diagnostic criteria for bvFTD, svPPA, and nfvPPA include neuroimaging as the major biomarker to aid in confident clinical diagnosis with an emphasis on structural magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) [1, 2].

Structural Magnetic Resonance Imaging

Structural MRI is widely used in clinical practice to visualize regional brain atrophy, with quantitative methods employed in research [3–7] and in some clinical practice settings [8]. In bvFTD, structural imaging studies consistently

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demonstrate atrophy patterns that implicate frontal (orbitofrontal, middle frontal gyrus, rostromedial prefrontal cortex, pre-supplementary motor cortex), insula (dorsal and ventral anterior insula extending to posterior insula at late stages), anterior/mid cingulate cortex (ACC/MCC), anterior temporal lobes and subcortical structures (basal ganglia, thalamus, hippocampus), as well as cerebellum (see Fig. 1) [9–11]. For review, see reference [6], and for meta-analyses, see references [12–14]. Despite a relatively predictable atrophy pattern, there remains considerable heterogeneity across patients. One study employed cluster analyses and identified four distinct neuroanatomical subtypes: frontal dominant, temporal dominant, frontotemporal, and distributed temporofrontoparietal [15]. A subcortical dominant subtype has also been described [16, 17]. Brain atrophy in fronto-insula-cingulate regions is present at the earliest stages of the disease, although less pronounced [9, 18]. The right temporal variant of FTLD has been variably characterized as semantic dementia or bvFTD but is generally associated with prominent behavioral symptoms, largely typical of bvFTD, often accompanied by prosopagnosia and semantic memory loss [19–22]. With time, atrophy progresses to include more distributed frontal, temporal, and insular cortices, as well as parietal regions and ventricular expansion (see Fig. 2) [9, 23–25]. Automated longitudinal MRI volumetry has demonstrated that structural MRI is sensitive to frontal atrophy progression in a period as short as 6 months after baseline [26].

Peak atrophy at baseline in svPPA has been reported in the anterior temporal pole (left > right hemisphere), extending to include frontoinsula, subgenual ACC, left middle and inferior temporal gyri, fusiform gyri, amygdala and basal forebrain (see Fig. 1) [12, 27–33]. In this regard, svPPA presents with similar atrophy distribution as the temporal dominant subtype of bvFTD with more atrophy in left relative to right hemisphere [15]. However, in contrast to bvFTD, svPPA has greater atrophy in the fusiform gyrus and relatively spared frontal as well as dorsal anterior

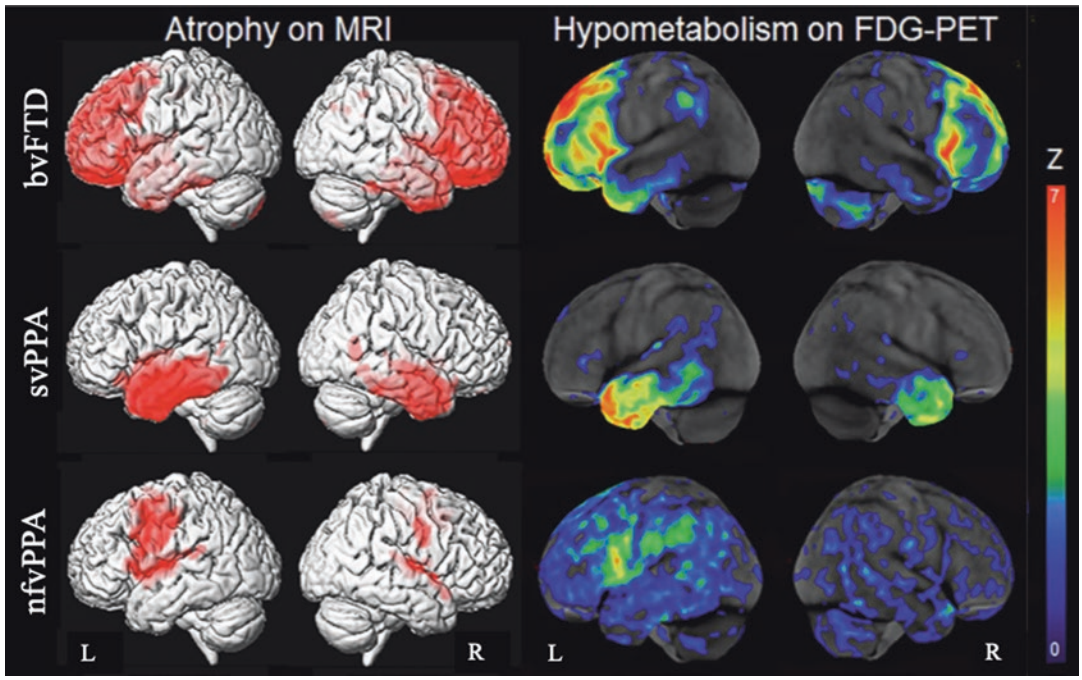

Fig. 1 Group-level patterns of atrophy and hypometabolism associated with FTLD clinical syndromes demonstrate similar patterns to single-subject scans (see Fig. 3). svPPA, semantic variant primary progressive aphasia; bvFTD, behavioral variant frontotemporal dementia; L, left; R, right. (Image adapted from Whitwell [17])

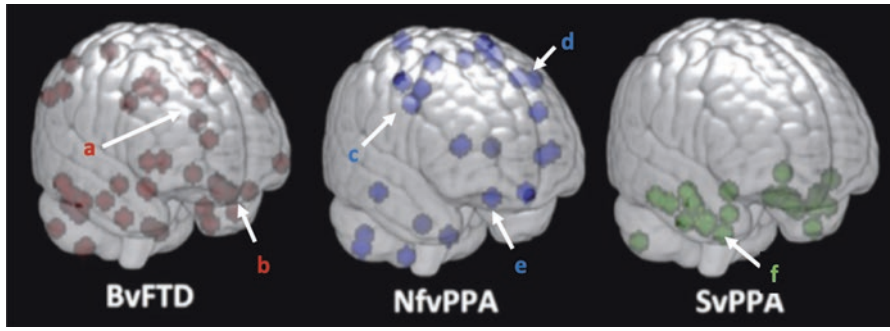

Fig. 2 Peak regions that display the highest rate of gray matter atrophy over a one-year follow-up. All three variants demonstrate differential patterns of longitudinal loss in gray matter volume, with highly clustered regions of change in svPPA (anterior temporal lobe) and more distributed changes in frontotemporal regions among bvFTD and nfvPPA variants. (**a**) dorsolateral prefrontal cortex; (**b**) orbitofrontal cortex; (**c**) premotor cortex; (**d**) superior frontal cortex; (**e**) inferior frontal gyrus (pars orbitalis); (**f**) anterior temporal lobe. (Image adapted from Binney, Pankov [53])

cingulate cortex [23, 34]. With disease progression, atrophy in svPPA becomes more distributed to include the middle and inferior frontal gyri, posterior temporal gyrus, and inferior parietal lobule [7, 28, 34–36]. Atrophy usually continues to be left-lateralized but spreads to homologous regions of the right hemisphere (see Fig. 2) [36, 37]. The rate of temporal gray matter loss can be 3–4% per six months [26], which is a higher rate of temporal atrophy than any other FTD variant [38].

In nfvPPA, peak atrophy is found in the inferior frontal gyrus, dorsolateral prefrontal cortex, and supramarginal gyrus of the left hemisphere (see Fig. 1) [32, 36]. Compared to both svPPA and bvFTD, nfvPPA demonstrates greater progressive atrophy in the parietal lobes [23] but relatively spared bilateral temporal pole, parahippocampal, entorhinal, fusiform, inferior temporal, middle, and left superior temporal gyrus [35]. Over time, atrophy in nfvPPA progresses to include more widespread left superior and middle frontal gyri, anterior insula, superior temporal gyri, transverse temporal gyrus as well as premotor areas, and caudate (see Fig. 2) [30, 31, 35, 36, 39]. In general, as atrophy progresses in both PPA variants, the pattern becomes less specific (though remains generally left-lateralized) and merges with each other to include major regions involved in language processing [40].

Within clinical settings, T1-weighted MRI is used nearly universally to increase confidence in the likely pathological changes in patients with these clinical syndromes [41]. In most clinical practice settings, planar images are inspected visually (see Fig. 3), which has been shown to be predictive of likely neuropathologic changes postmortem [42]. Although not yet routinely used in clinical practice, a variety of fully automated, observer-independent atrophy quantification methods have been developed, including voxel-based morphometry, single-subject whole-cortex general linear models, and machine learning–based individual subject classification models [26, 32, 42–45]. A few of these methods are beginning to be employed in clinical practice settings [46, 47].

A number of studies have examined the sensitivity and specificity of quantitative analysis of MRI volumetrics for diagnosis. In a recent multicenter structural MRI study, Meyer and Mueller [48] applied pattern recognition algorithms to regional brain atrophy and predicted diagnosis of bvFTD (vs. healthy controls) with high accuracy of up to 84.6%. In another study, gray matter density-based machine learning classification of bvFTD versus Alzheimer's disease (AD) outperformed the classification that was based on neuropsychological test results [49]. Similarly, diagnostic criteria for PPA sup-

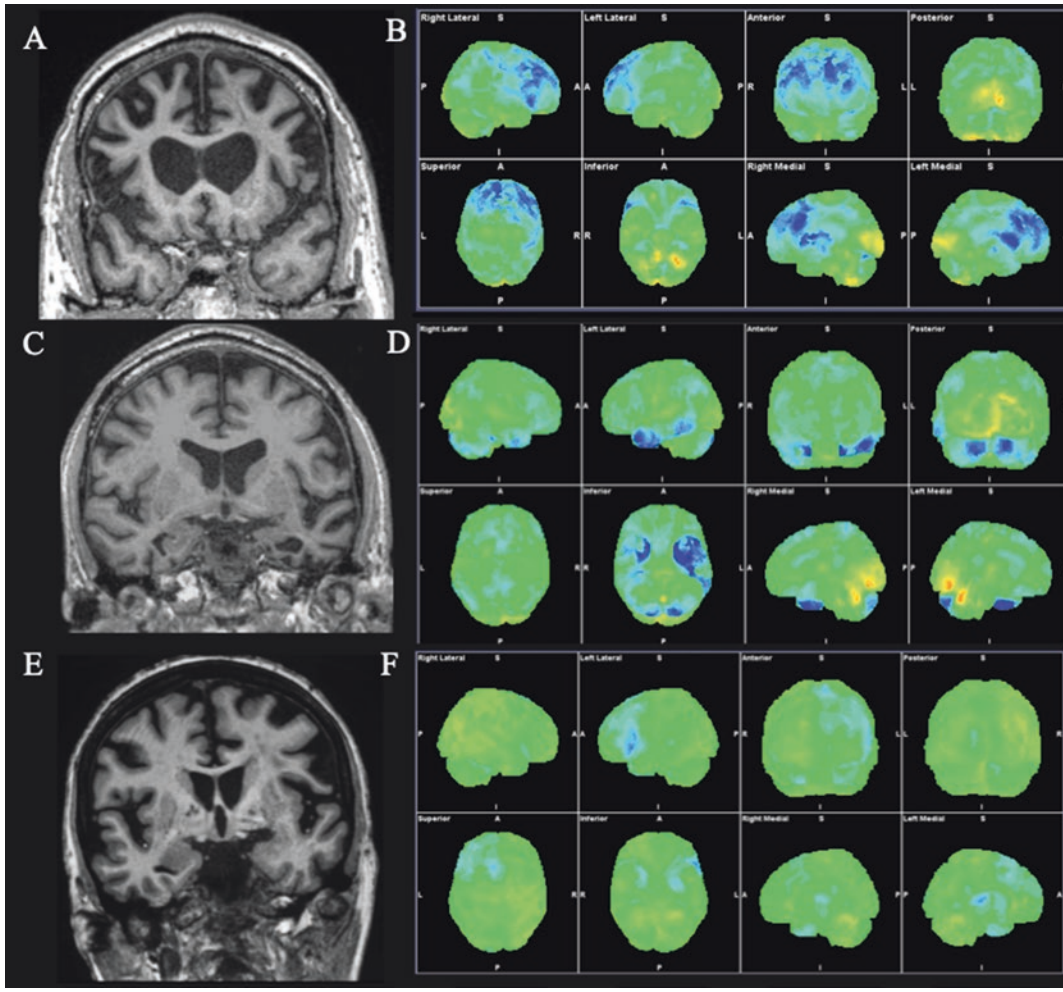

Fig. 3 T1-weighted MRI images and FDG-PET surface projections obtained in clinical practice in individual patients with typical FTLD clinical syndromes. In bvFTD, atrophy (**a**) and hypometabolism (**b**) are observed in bilateral dorsolateral and dorsomedial prefrontal, anterior and mid-cingulate, and insular cortices. BvFTD is heterogeneous, and patients often present with orbitofrontal or right anterior temporal atrophy. In svPPA, atrophy (**c**) and hypometabolism (**d**) are most notable in anterior temporal lobe (L > R) regions and extend to left lateral temporal cortices. In nfvPPA, atrophy (**e**) and hypometabolism (**f**) are seen in left insular cortex, inferior and middle frontal gyri, and the amygdala

port patterns of brain atrophy specific to the regions outlined earlier. Recently, MRI-based cortical thickness was shown to classify a single patient as belonging to one subtype of FTD with high accuracy: 86% healthy controls versus dementia (FTD and AD), 90.8% of AD versus FTLD, 86.9% bvFTD versus PPA, and 92.1% svPPA versus nfvPPA [44]. Atrophy in right frontotemporal regions successfully discriminates bvFTD from PPA, atrophy in the left frontal lobe discriminates nfvPPA from svPPA, and atrophy in the bilateral anterior temporal cortex discriminates svPPA from bvFTD and nfvPPA [44, 50]. Another study reported a similar high accuracy (78%) of discrimination between svPPA and nfvPPA [43]. Despite the high predictive power of structural MRI in distinguishing FTLD subtypes from each other and from

other neurodegenerative diseases, more research is needed to validate findings in unselected cases in clinical practice settings [51, 52].

Studies are underway to identify the best MRI measures that could serve as clinical trial endpoints in FTLD. Findings are variable without clear convergence on optimal regions of interest across FTLD variants [24, 53]. Even within variants, differences in peak atrophy across patients impact effect sizes. Binney and Pankov [53] estimated a sample size of 103 bvFTD, 31 nfvPPA, and 10 svPPA to be able to detect a 40% reduction in annual rate of regional atrophy. In that study, the most sensitive regions of interest were the medial and lateral frontal gyri; the insula, striatum, and temporoparietal junction bilaterally for bvFTD; the superior and ventral anterior temporal, mid-to-posterior lateral temporal, and medial frontal cortices for svPPA; and the dorsomedial and lateral frontal cortices with predominant involvement of the precentral and perisylvian regions for nfvPPA. A study of PPA [40] with all three major subtypes found that atrophy in the left perisylvian temporal cortex, including insula and surrounding temporal regions, may be a highly sensitive measure of disease progression and a promising endpoint for clinical trials. As small as ten participants per arm could have 80% power to detect 40% slowing of atrophy [40]. A follow-up proof-of-concept study of optimal MRI endpoints in clinical trials in PPA further found that a composite with weighted averages of regional volumes within the left perisylvian temporal cortex can reduce sample size relative to total region of interest (ROI) by 38% [54]. Most recently, Staffaroni and Ljubenkov [55] reported that gray matter volume in frontal and temporal lobes predicted longitudinal change across all FTLD subtypes. Further, sample size predictions to detect a 40% reduction in decline following a therapeutic intervention (54 bvFTD, 34 svPPA, and 29 nfvPPA) were better than or comparable to estimates for clinical measures alone (e.g., functional assessment questionnaire). Notably, bvFTD yielded the largest confidence intervals across all measures and metrics of white matter integrity (discussed later) yielded the smallest predicted sample sizes.

Fluorodeoxyglucose Positron Emission Tomography

PET with 18F-fluorodeoxyglucose tracer enables the quantification of cerebral glucose metabolism as a proxy measure of neural activity. This biomarker has been found to have greater sensitivity and specificity to neurodegeneration relative to measures of perfusion using single-photon emission computed tomography (SPECT; [56]), although SPECT is more widely available. Patterns of hypometabolism in FTLD generally precede and correlate with the spread of atrophy (see Fig. 1) [57]. In samples with bvFTD, hypometabolism has been identified in the orbitofrontal, dorsolateral and medial prefrontal, insular, and cingulate cortices [58, 59]. Subcortical structures, particularly the caudate nucleus, are also affected [60–62]. Cluster analyses have delineated two bvFTD subgroups with frontal (dorsolateral, medial, and ventromedial prefrontal cortices) and temporal-limbic (temporal poles, hippocampal formation, lateral temporal cortex, amygdala, thalamus) hypometabolic signatures. The frontal subgroup was associated with greater executive dysfunction and a faster rate of clinical decline, suggesting that differential patterns of hypometabolism can predict clinical outcomes [63, 64]. However, less is known about metabolic changes with disease progression. Some evidence suggests that over a 1–2-year follow-up period, worsening hypometabolism is observed in regions implicated at baseline, accompanied by a progression of hypometabolic activity into inferior frontal, parietal, and temporal regions [58, 65].

Among PPA variants, reduced metabolism is primarily left lateralized, particularly earlier in the disease. Hypometabolism in svPPA has been most consistently reported in the temporal poles, middle and inferior temporal gyri, and insula [63, 66, 67], with some studies also demonstrating

thalamic [68], medial temporal (hippocampus and amygdala), fusiform, and superior temporal involvement. nfvPPA is associated with a heterogenous metabolic pattern [69], with evidence of hypometabolism in superior and inferior (particularly the pars opercularis and pars triangularis) frontal, dorsolateral prefrontal, anterior cingulate, and insular regions [67, 70]. Reduced metabolic activity in the thalamus and temporal cortices has also been reported (See Fig. 1) [68]. Hypometabolism spreads posteriorly toward the precentral gyrus in those with nfvPPA who progress to develop parkinsonism and toward the anterior temporal lobe in those who developed motor neuron disease [67].

FDG-PET has been approved for reimbursement by the US Center for Medicare Services, but, unfortunately, many private insurance companies still do not reimburse for its use in the US. Consensus groups have identified FDG-PET as an effective and recommended diagnostic tool to identify FTLD (see Fig. 3) [71] and differentiate FTLD from AD or Lewy body disease pathology [72]. Utilizing FDG-PET to identify FTLD in mild cognitive impairment (MCI) stages is also recommended, though this is understudied and requires additional formal investigation [73]. Visual assessments of FDG-PET scans in a clinical setting are generally accurate, with 89.6–92% accuracy, 81–86% sensitivity, and 94–98% specificity, in the differential diagnosis between AD and FTLD [74, 75]. The distinguishing pattern of hypometabolism that informs this differential follows a dissociation between anterior and posterior cortical areas, with reduced metabolic activity in frontal, but not posterior, regions predicting FTLD pathology [76]. Statistical regions of interest and parametric mapping analyses improve diagnostic accuracy and further underscore the utility of this biomarker in clinical settings [74, 77–80]. Only a small handful of studies have investigated the diagnostic utility of FDG-PET in PPA variants, but these have provided compelling evidence supporting its use in clinical settings [81]. One study found that visual ratings resulted in 87.8% sensitivity and 90% specificity to differentiate between PPA and cognitively normal patients; statistical analyses improved these numbers to 95.70–96.9% and 90%, respectively [82]. The diagnostic accuracy of using FDG-PET to differentiate between PPA variants also yields sensitivity, specificity, and accuracy values above 90% [82]. A number of case studies have also documented the utility of FDG-PET in diagnosing PPA [83, 84].

Amyloid Positron Emission Tomography

PET imaging with amyloid tracers measures insoluble fibrillar amyloid, largely reflecting neuritic plaques, one of two core neuropathologic changes seen in AD. Amyloid PET has little clinical utility in the evaluation of a patient with a typical presentation of nfvPPA, svPPA, or bvFTD. Its primary value is in patients presenting with a dysexecutive-behavioral or complex language syndrome that is not typical of FTLD or AD, but where AD is a possibility [85, 86]. Most experts would recommend that FDG-PET be performed first, and if the case is still ambiguous, amyloid PET could be considered. The important challenge, though, is that even though amyloid PET is approved by the US Food and Drug Administration and by the European Medicines Agency, reimbursement is generally not available outside the context of research. An amyloid PET scan showing elevated signal in a patient with a typical FTLD clinical syndrome may be an indicator that AD is a coexisting pathologic change along with FTLD [87, 88]. Comorbid AD and FTLD pathologies are not infrequent [89], especially in older age. Analyses of elevated signal on amyloid PET in svPPA and nfvPPA have generally concluded that the frequency of "positive" amyloid PET scans increase with age at the same rate as in cognitively normal adults [90–92]. Thus, amyloid PET imaging may be useful in clinical settings with complicated cases in which AD remains on the differential diagnosis after comprehensive workup, but it is not considered a routine element of the workup of a patient with a typical FTLD clinical syndrome.

Multimodal Imaging in Frontotemporal Lobar Dementia in Clinical Practice

A multimodal approach to differential diagnosis appears to improve classification accuracy, particularly when integrating structural and metabolic imaging. The combination of T1-weighted MRI and FDG-PET imaging (see Fig. 3) distinguishes between other neurodegenerative disorders and bvFTD with 82.5% accuracy, svPPA with 97.5% accuracy, and nfvPPA with 87.5% accuracy [93]. Combined T1-weighted MRI and FDG-PET also distinguish between bvFTD and psychiatric disease with 96% sensitivity and 73% specificity, suggesting that this approach may reduce the number of bvFTD patients that are misdiagnosed with psychiatric illness [49]. Ultimately, sensitive and specific molecular biomarkers are badly needed for these conditions.

Imaging Modalities Utilized in Research Contexts Only

Although not yet used clinically, there are a number of additional informative neuroimaging modalities that can elucidate the pathophysiology underlying FTLD, inform differential diagnosis, and, in some cases, have the potential to be valuable in clinical trials. These include diffusion tensor imaging (DTI), resting-state functional MRI (rs-fMRI), arterial spin labeling (ASL) MRI, and tau PET.

Diffusion Tensor Imaging

DTI characterizes white matter microstructural integrity by measuring directionality (fractional anisotropy [FA]) and diffusivity (mean diffusivity [MD]) of water molecules along white matter tracts. Decreased FA and increased MD suggest degeneration of white matter fibers and compromised structural connectivity within the brain. There is a robust literature demonstrating widespread alterations in white matter tracts in FTLD (see Fig. 4). When compared to both AD and control groups, bvFTD is associated with bilateral white matter alterations in tracts underlying frontal and temporal lobes [94]. Studies have demonstrated either reduced FA or increased MD in the superior longitudinal fasciculus, anterior cingulum, corpus callosum, and uncinate fasciculus [95–98]. The inferior longitudinal fasciculus and inferior fronto-occipital fasciculus, along with fronto-striatal and fronto-thalamic pathways, have also been implicated [94, 99–102]. Longitudinal studies have demonstrated progression of abnormalities in these tracts, particularly in the uncinate fasciculus, corpus callosum, and paracossal cingulum [103, 104], and suggest that further progression to parietal and occipital white matter can be expected [105]. White matter alterations in bvFTD are associated with greater behavioral symptom severity [96, 100] and reduced integrity in the corpus callosum over a 2-year follow-up is associated with a decline in executive functioning [104], further underscoring the value of this modality in tracking disease progression in bvFTD.

In contrast, the PPA subtypes demonstrate more focal white matter alterations in tracts that originate from and terminate in brain regions important for language. svPPA is associated with relatively circumscribed alterations to white matter in ventral pathways projecting to the left temporal lobe early in the disease, with particular emphasis on uncinate and inferior longitudinal fasciculi [54, 70, 94, 106]. Reduced FA in the external capsule and cingulum bundle has also been reported [107]. With disease progression, further degeneration extends bilaterally to the nondominant frontotemporal, uncinate, and anterior inferior longitudinal fasciculi [54, 108, 109]. Cross-sectional alterations in nfvPPA relative to control samples are most notable in left frontotemporal and frontoparietal projections of the superior longitudinal and uncinate fasciculi [54, 94]. Alterations in the frontal aslant tract and in white matter projections from the basal ganglia to premotor and motor cortical areas have also been reported [70, 106, 110, 111]. Over time, white matter degeneration in both PPA variants spread from left to right hemisphere, though posterior tracts remain relatively spared [54].

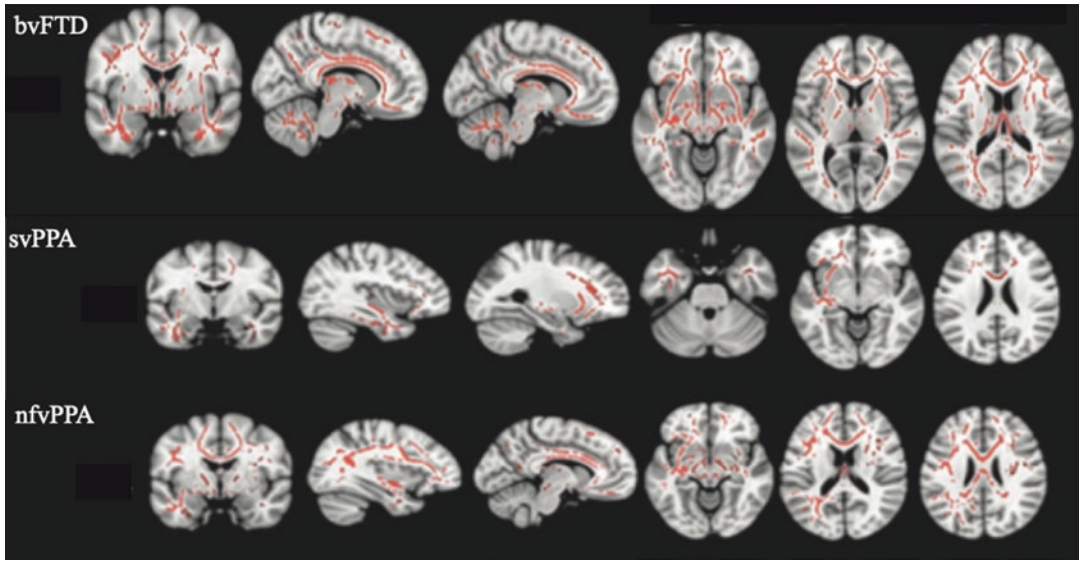

Fig. 4 Diffusion tensor imaging demonstrates white matter abnormalities in tracts projecting to and from regions atrophied in each variant. bvFTD is associated with widespread bilateral white matter changes in orbitofrontal and anterior temporal tracts (i.e., corpus callosum, inferior and superior longitudinal fasciculi, anterior thalamic radiation, and uncinate fasciculus). White matter changes in svPPA are seen primarily in the temporal lobe (i.e., anterior portions of the inferior longitudinal fasciculus and the uncinate fasciculus, L > R). In nfvPPA, white matter changes are observed in frontotemporal tracts (i.e., superior and inferior longitudinal fasciculi and corpus callosum). (Image adapted from Lam, Halliday [105])

Although not used clinically, DTI has proven to be a promising biomarker to inform differential diagnosis and monitor disease progression in FTLD. FA in the corpus callosum and uncinate fasciculus is particularly helpful in differentiating between FTLD and controls [112], AD patients [113], and among FTLD variants [95]. Some studies have shown that DTI outperforms structural gray matter volumetric and FDG-PET in differentiating bvFTD from controls [114] and from other FTLD variants at the group level [115]. However, another study found that DTI remains less sensitive than FDG-PET at the single subject level [116]. Further studies are needed to evaluate the potential added value of combining DTI with structural MRI or FDG-PET. Specifically, FA in the corpus callosum and gray matter volume in the precuneus and posterior cingulate provided optimal classification between a combined FTLD group and AD. A similar white and gray matter solution was found to optimally distinguish between FTLD variants, yielding classification accuracies of 90% in bvFTD, 80% for svPPA, and 100% for nfvPPA [5, 117]. A combination of gray (left temporal pole and pars opercularis) and white matter (left uncinate and inferior longitudinal fasciculi) structural integrity also appears to maximally distinguish between PPA variants with 89% accuracy, 92% sensitivity, and 85% specificity [118]. Finally, with regard to clinical trials, DTI measures of corpus callosum integrity are potential clinical trial endpoints that requires the smallest sample sizes to detect clinical change [55, 112]. Thus, while it is unlikely that DTI will take the place of traditional neuroimaging biomarkers currently used in clinical settings, it may offer additive value that is worth further investigation in the context of clinical trials.

Resting-State Functional Magnetic Resonance Imaging

rs-fMRI measures intrinsic functional connectivity between brain regions to detect synchronous

patterns of low-frequency fluctuations in blood oxygen level–dependent signals. From a network perspective, this modality has been critical in identifying groups of brain regions in healthy populations that are functionally related yet spatially distinct [119–122]. In general, rs-fMRI studies in FTLD demonstrate altered connectivity in established networks that closely follow distributed atrophy patterns identified in FTLD (see Fig. 4).

The most robust finding in bvFTD is reduced functional connectivity within the salience network [123–125], with primary nodes in the ACC/MCC, frontoinsula, middle frontal gyrus, and subcortical regions in the striatum and amygdala [120, 121]. Abnormalities in this network are associated with compromise in behavioral and socio-emotional functioning that are a hallmark of bvFTD [121, 126]. Reduced connectivity between frontal and limbic structures within the salience network has also been observed [125, 127, 128]. Paralleling other reports of neuroanatomical and functional subgroups within bvFTD, Ranasinghe and Rankin [16] reported four distinct patterns of network dysfunction encompassing the frontotemporal dominant salience network, frontal dominant salience network, a subcortical network, and a semantic appraisal network (temporal pole, ventral striatum, subgenual cingulate, and basolateral amygdala). Graph theory models have documented a decline in major network nodes in frontotemporal regions with relative sparing of posterior cortical areas [129, 130]. Indeed, several studies have demonstrated either equivalent or even increased connectivity within the default mode network relative to controls and AD, suggesting the possibility of a compensatory response in the context of alterations in frontotemporal networks [124, 131]. Over time, however, network disruption does progress posteriorly to involve frontoparietal and default mode networks [132].

Alterations in rs-fMRI also closely follow atrophy patterns among PPA variants. Consistent with the posterior-medial anterior-temporal framework proposed to dissociate regions underlying semantic and episodic memory [133], networks anchored in anterior temporal regions important for semantic memory appear to be most vulnerable to disruption in svPPA. Specifically, there is reduced connectivity between the anterior temporal lobe and distributed cortical and subcortical areas, including modality-specific cortical regions, which support the role of the anterior temporal lobe as a critical transmodal hub within the semantic network (see Fig. 5) [33, 134, 135]. Others have documented decreased connectivity and reduced network hubs in ventral regions of (i.e., middle temporal gyrus and angular gyrus), while increased connectivity in more dorsal regions were observed (i.e., inferior frontal gyrus and superior portion of angular gyrus) [136–138]. Only a small handful of studies have investigated functional connectivity in nfvPPA; these have documented reduced connectivity within the speech and language network (SLN), which encompasses left inferior frontal, dorsal insular, supplementary motor, and inferior parietal regions, that are responsible for speech and language production [119]. Relative to control samples, nfvPPA patients demonstrate reduced connectivity within this network, but not among regions belonging to the default mode network [139]. Research designs employing graph theory to characterize nodes within the SLN report reduced efficiency and number of nodes, particularly in left parietal regions [140, 141].

There is also a growing body of literature demonstrating the utility of rs-fMRI in predicting future atrophy in FTLD. Network disruption in svPPA and nfvPPA among key nodes of language networks identified in control samples predict longitudinal gray matter thinning in those regions in respective patient groups [33, 140], suggesting that neurodegeneration may propagate along functional pathways in large-scale networks (see Fig. 5). Building on this work, Brown and Deng [142] demonstrated that individualized "epicenters" of atrophy at baseline (i.e., atrophied regions whose functional connectivity guides disease spread within a network) in bvFTD (anterior cingulate and frontoinsular cortex), and svPPA (anterior temporal lobe) predicted longitudinal gray matter loss for patients in mild-to-moderate clinical stages.

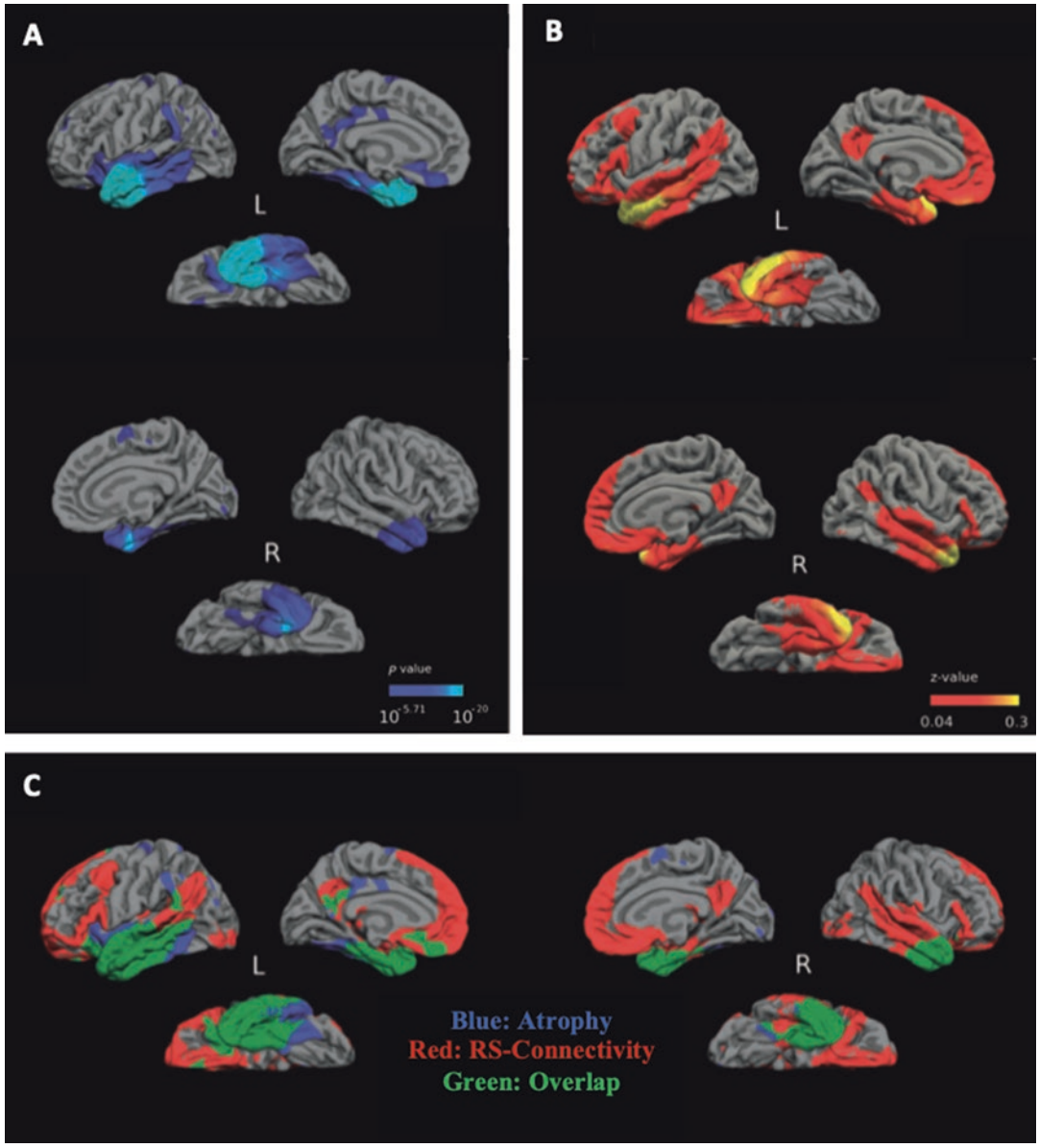

Fig. 5 Network-specific degeneration in svPPA. The temporal pole area of greatest atrophy in svPPA (**a**) anchors a large-scale intrinsic functional connectivity network important for semantic cognition (shown in healthy adults, **b**), which overlaps with the pattern of cortical atrophy in svPPA (**c**, overlap shown in green). (Image created from data published in Collins, Montal [33])

Brain atrophy tends to spread from the epicenter to its neighboring and adjacent functionally connected regions that also exhibit some intermediate atrophy at the baseline MRI. These findings support the possibility for rs-fMRI to be utilized as a marker to make individualized predictions of future gray matter loss in FTLD, but this has not yet been fully investigated.

The few studies that describe the utility of rs-fMRI to inform differential diagnosis in clinical

settings have focused on bvFTD and AD samples. bvFTD is associated with network disruption more specific to frontal and temporal nodes, while studies in AD demonstrate more widespread global alterations of network connectivity with preferential involvement of posterior regions [143]. This pattern has been demonstrated to distinguish between bvFTD and AD with 92% accuracy [124]. Introducing rs-fMRI to a multimodal solution appears to yield mixed results. One study documented only a small improvement in distinguishing between bvFTD and control participant using a multimodal solution that incorporated morphometric features (i.e., temporal and frontal gray matter volume) and network connectivity between and within frontal, temporal, and parietal nodes [144]. In contrast, the combination of rs-fMRI, DTI, and structural MRI was found to provide the strongest diagnostic classification between AD and bvFTD [145].

Arterial Spin Labeling

ASL is an MRI sequence that magnetically labels arterial water as an endogenous tracer to quantify cerebral blood flow (CBF). This method offers several advantages over traditional PET/SPECT perfusion methods, as it is less expensive, has shorter acquisition times, and does not require intravenous contrast agents. Despite its promise, only a small handful of studies have utilized ASL techniques to assess CBF in sporadic FTLD. These studies have documented hypoperfusion in frontal lobes and the anterior cingulate cortex in bvFTD (see Fig. 6) [62, 146, 147]. svPPA is associated with hypoperfusion in the left temporal lobe and insula, and hyperperfusion in the right superior temporal, inferior parietal, and orbitofrontal cortices. Alterations in CBF adjacent to regions that were atrophied at baseline predict subsequent gray matter loss at follow-up [148], suggesting a role for this modality in predicting future regional cortical degeneration.

Evidence to date suggests that ASL may be useful in differentiating between FTLD and AD patients. Similar to other modalities discussed in this chapter, perfusion between these two patient populations appears to follow an anterior-posterior dissociation; FTLD cases demonstrate frontotemporal hypoperfusion, while AD patients exhibit hypoperfusion in parietal regions [146]. One study reported that whole-brain ASL accurately classified bvFTD and AD groups with 83% sensitivity and 93% specificity [149], while another reported 77% sensitivity and 76% specificity in the precuneus [147]. Two studies have suggested that ASL and FDG-PET have equivalent diagnostic utility [62, 149, 150], while another found reduced classification accuracy with ASL relative to FDG-PET [151]. Thus, ASL imaging in FTLD is relatively understudied but merits further investigation to better document its clinical value relative to other modalities.

Tau Positron Emission Tomography

In 2013, when Brad Dickerson was putting the final touches on editing Hodges' Frontotemporal Dementia [152], we were so enthusiastic about the potential of new radioligands for measuring tau in the living human brain that we put our first FTD patient's scan on the cover of the book. This was a patient with *MAPT* P301L-related mild-stage FTD who had clearly elevated signal in all of the right places. Similar enthusiasm was generated when we saw our first nfvPPA and our first progressive supranuclear palsy (PSP) case. Unfortunately, when we presented a summary of our first series of cases at the Human Amyloid Imaging meeting in Miami in 2014 [153], we also had to reveal that we saw substantially elevated signal in a *GRN*-related FTD patient and in a svPPA patient, both of whom eventually were confirmed by autopsy not to have FTLD tau pathology, but rather the expected FTLD TDP43 pathology. Looking back at the accrued knowledge from the perspective of the Tau 2020 meeting in Washington D.C., where Gil Rabinovici presented a masterful summary of tau PET in the non-Alzheimer dementia spectrum [154], we have learned a number of specific lessons. First, the current generation of tau PET tracers works

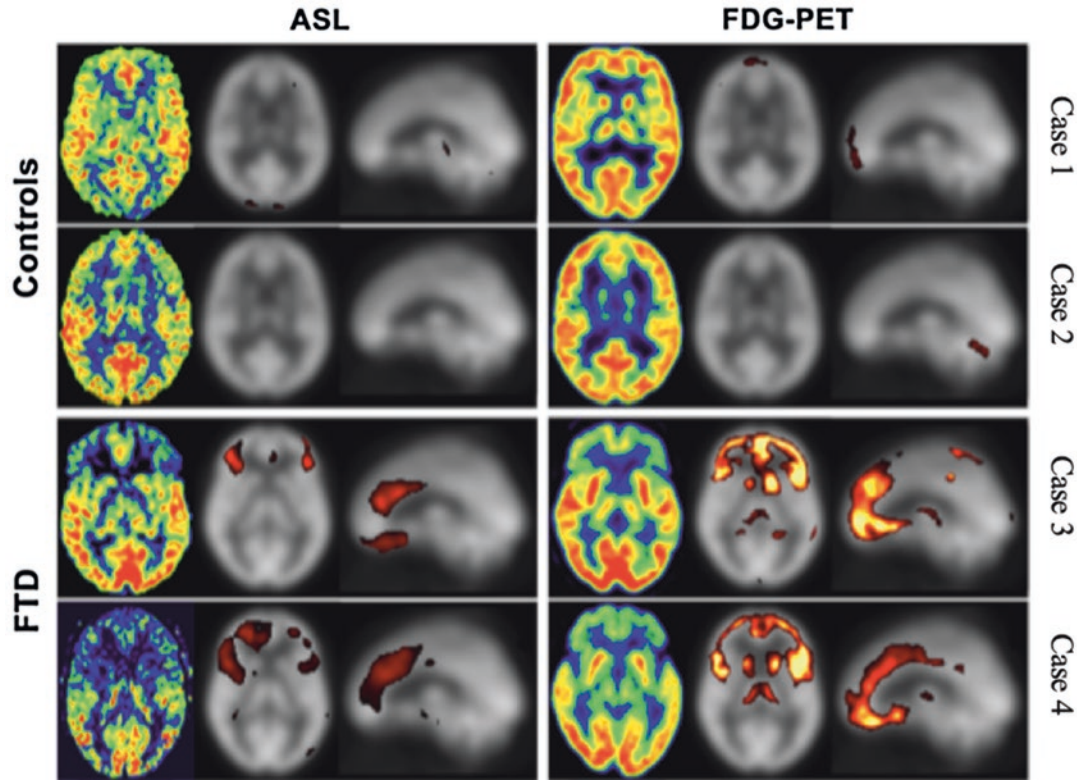

Fig. 6 Single-subject images showing ASL and FDG-PET in control (cases 1 and 2) and bvFTD (cases 3 and 4) participants. For each modality, the two right columns show statistical comparisons to controls. Correlations between hypoperfusion in ASL and hypometabolism in FDG-PET have led some investigators to suggest that ASL, collected in an MRI session with other sequences, could potentially serve as a surrogate for FDG-PET. (Image adapted from Fällmar, Haller [150])

generally very well for measuring AD-related paired helical filament tau pathology [155], and there appears to be weak, but topographically appropriate, signal in PSP [156] and CBS likely due to CBD pathology [157]. And in *MAPT* mutation carriers, signal is more elevated in those with mutations associated with tau aggregation that has conformational shapes more similar to those of AD (e.g., the R406W mutation) [158, 159]. But there is also consistently elevated signal in svPPA [160–163] and variably elevated signal in *GRN*-related or *C9orf72*-related FTLD, calling into serious question the specificity of binding of the first tracers to tau pathology. Furthermore, autoradiographic studies show little or no binding of as ^{18}F-Flortaucipir or as ^{18}F-MK6240 to FTLD tau pathology [164–168]. Some of this can be understood with our advancing knowledge of the 3D shape of tau inclusions and other work on the fundamental biology of tau by pioneers, including Michel Goedert and Maria Grazia Spillantini and Bernardino Ghetti and colleagues [169–172].

Thus, while advances in tau PET imaging over the past 7 years is tremendous and is having a prominent impact on the AD field, its value in FTLD is not yet clear and will require substantial further work which is ongoing [173, 174]. There also remains an urgent need to develop imaging biomarkers of FTLD TDP-43, and work is ongoing to try to measure glial cell responses that may contribute to FTLD-related neurodegeneration [175].

Conclusions

Recent advances in neuroimaging have enabled a more complete understanding of the pathophysiology of FTLD and have offered improved diagnosis of sporadic clinical syndromes associated with FTLD. Overwhelmingly across all modalities, abnormalities in brain structure and function have been identified predominantly in frontal, temporal, and subcortical areas, with eventual progression posteriorly. At present, gray matter morphometry and glucose metabolism, captured by structural MRI and FDG-PET, respectively, appear to have the most robust evidence supporting differential diagnosis in clinical settings. However, multimodal imaging protocols are gaining traction and may serve to improve diagnostic accuracy and longitudinal monitoring, particularly when including DTI and/or rs-fMRI.

Substantial multicenter efforts are underway to identify ideal biomarkers that are sensitive to preclinical stages, track disease progression, and predict underlying pathology, particularly the Genetic Frontotemporal Dementia Initiative (GENFI) [176, 177] and the Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL)/Longitudinal Evaluation of Familial Frontotemporal Lobar Dementia Subjects (LEFFTDS)/Longitudinal Frontotemporal Lobal Degeneration (ALLFTD) [178] initiatives. While these and many other smaller studies are ongoing, evidence to date supports the value of a variety of imaging biomarkers in clinical trials, aiming to develop novel therapeutics for these devastating diseases.

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The Frontotemporal Dementia Prevention Initiative: Linking Together Genetic Frontotemporal Dementia Cohort Studies

Jonathan D. Rohrer and Adam L. Boxer

Introduction to Genetic Frontotemporal Dementia

Pathogenic mutations are found in around 25–30% of people diagnosed with frontotemporal dementia (FTD). This percentage is higher in those with the behavioural variant (bvFTD) where it is about 40%, and much lower in those with the language variant (known as primary progressive aphasia, PPA) where it is around 5% [7]. Mutations in three genes (*MAPT*, *GRN* and *C9orf72*) account for the majority of genetic frontotemporal dementia, with all having an autosomal dominant pattern of inheritance. However, mutations have also been found less frequently in a number of other genes (*TBK1, VCP, TARDBP, SQSTM1, FUS, CHMP2B*), with individual or limited reports in further genes (*CHCHD10, UBQLN2, OPTN, CCNF, DCTN, TIA1*).

The prevalence of genetic frontotemporal dementia has been poorly studied. Prior studies of FTD as a whole have mainly focused on specific age groups with an estimated point prevalence between the ages of 45 and 64 of 15–22 per 100,000 [15]. However, a recent study in the UK estimated a prevalence across all ages of 11 per 100,000 [5]. Worldwide, around 40% of genetic FTD cases have mutations in *C9orf72,* 35% in *GRN* and 25% in *MAPT*, with only 1–2% having mutations in the other genes [13]. If 30% of FTD is genetic, this equates to a prevalence of ~1.3 per 100,000 (e.g. ~4745 people in North America) for *C9orf72*-related FTD, ~1.2 per 100,000 (e.g. ~4380 people in North America) for *GRN*-related FTD and ~ 0.8 per 100,000 (e.g. ~2920 people in North America) for *MAPT*-related FTD. Overall, prevalence numbers relate to symptomatic mutation carriers, but as their siblings and children are at 50% risk of developing symptoms, there exists a larger population of living presymptomatic mutation carriers as well.

Multicentre Genetic Frontotemporal Dementia Cohort Studies and the Development of the Frontotemporal Dementia Prevention Initiative

Families with genetic FTD have been studied in case reports and series from individual centres over many years (reviewed in [18]). However, given the rarity of genetic FTD, it became

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clear that centres would need to collaborate more closely, in order to better understand the disease, building a joint methodological platform to create a cohort of genetic FTD mutation carriers, and develop robust biomarkers of disease onset and progression. In 2012, a group of centres specializing in FTD within Europe and Eastern Canada came together to create the Genetic FTD Initiative (GENFI). Following this, in 2015, centres in the United States and Western Canada created the overlapping Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) and Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) studies. More recently, genetic FTD cohort studies in Australia (Dominantly Inherited Non-Alzheimer Dementias study, DINAD), New Zealand (NZ FTD Genetic Study, FTDGeNZ) and South America (Research Dementia Latin America, ReDLat) have either got started or will be starting soon.

Recognizing the importance of working together across the world, GENFI and ARTFL-LEFFTDS (now ALLFTD) investigators have come together to create the FTD Prevention Initiative (FPI). The overall goal of the group is to work together to promote clinical trials of new therapies to prevent FTD, with the key aims of:

1. Creating an international database of familial FTD research participants who might be eligible for clinical trials
2. Creating uniform standards for the conduct of clinical trials in familial FTD syndromes

The FPI recognizes the importance of involving families with genetic FTD, with patient advocacy groups and foundations involved in FTD research such as the Association for Frontotemporal Degeneration, Bluefield Project to Cure FTD and the FTD Disorders Registry, also part of the initiative.

In this chapter, we describe, firstly, the initial FPI project, which investigated age at symptom onset and disease duration as well as phenotype in genetic FTD [13]; secondly, the current status of outcome measures for genetic FTD trials (mainly relating to work from the GENFI and ARTFL-LEFFTDS studies) and, lastly, the ongoing and planned trials in genetic FTD.

Other projects that are ongoing as part of the FPI include:

1. Modelling disease progression in genetic FTD with cognitive, brain imaging and fluid biomarkers
2. Predicting phenoconversion to symptomatic FTD
3. Understanding variability in bioassays for progranulin
4. Surveying participants to understand what family members want from genetic FTD trials

Phenotype, Age at Onset and Disease Duration in Genetic Frontotemporal Dementia

The first FPI study bringing together data from across the world on the three main forms of genetic FTD was recently published [13]. From data on 3403 symptomatic individuals with *C9orf72, GRN* and *MAPT* mutations, the project reported a number of key findings:

1. A total of 130 different *GRN* mutations and 67 different *MAPT* mutations are described in the paper, with the most common mutations being T272fs, R493X, IVS7-1G > A, C31fs, G35fs and A9D in *GRN*, and P301L, IVS10 + 16C > T, R406W and N279K in *MAPT*. An updated list of genetic mutations can be found at www.ftdtalk.org/what-is-ftd/genetics/.
2. Geographical variability exists in the distribution of the main genetic FTD groups, with an increased prevalence of *GRN* mutations in some countries, for example, Italy, Spain and Belgium, mainly due to large founder families (T272fs, IVS7-1G > A and IVS1 + 5G > C, respectively). Large *MAPT* families also exist, for example, IVS10 + 16C > T, originally from the North Wales area of the UK, and the PPND family with the N279K mutation.

3. The most common phenotype in each form of genetic FTD is bvFTD. PPA is a more common diagnosis in *GRN* mutation carriers (20%) with the specific variant usually being non-fluent variant PPA or a mixed PPA syndrome, compared with *MAPT* (6%) or *C9orf72* (4%). Corticobasal syndrome is seen not uncommonly in the *GRN* group (6%), to a lesser extent in the *MAPT* group (3%) and only rarely in the *C9orf72* group. In comparison, a classical PSP syndrome (i.e. Richardson's syndrome) is seen in 6% of *MAPT* mutation carriers, but not in the *GRN* group and only in rare cases in *C9orf72* expansion carriers. Amyotrophic lateral sclerosis (ALS) is only a very rare occurrence in *GRN* (2%) or *MAPT* mutation carriers (1%), whereas around 40% of *C9orf72* expansion carriers have either pure ALS (26%) or an FTD-ALS overlap (15%).
4. A wide range of age at symptom onset exists across all of the genetic groups, with onset between the 20s and the 90s for *GRN* and *C9orf72* groups, and from 17 to the 80s in the *MAPT* group (Fig. 1a). There is little difference in age at onset across the different *GRN* mutations (Fig. 1b), but there are key differences across the common *MAPT* mutations, with those with N279K mutations having a lower age at onset (mean 43.8 years), followed by IVS10 + 16C > T (50.9), then P301L (53.0) and, finally, R406W (55.4), having the oldest mean age at onset (Fig. 1c).
5. In all three genetic groups, being given a diagnosis of 'Alzheimer's disease' was associated with an older age at onset, whilst, in *MAPT* mutations, individuals with atypical parkinsonian syndromes were younger at onset.
6. Disease duration was lowest overall in those with *C9orf72* mutations, followed by those with *GRN* and then *MAPT* mutations. In the *C9orf72* group, a diagnosis of ALS was associated with a shorter disease duration (mean 2.9 years) than FTD-ALS (5.0), PPA (7.5) and bvFTD (7.8).
7. Individual age at onset correlated with mean age at onset within the family in all three groups (*C9orf72*, r = 0.36; *GRN* r = 0.18; *MAPT* r = 0.63), as well as with parental age at onset (*C9orf72*, r = 0.32; *GRN* r = 0.22 *MAPT* r = 0.45) (Fig. 2), with the correlation strongest in *MAPT* mutations.
8. Variability in age at onset was explained largely by family membership and the specific mutation in *MAPT* mutations, but not in the *GRN* or *C9orf72* groups.

Overall, the study provides important data that will be useful for future trials. In particular, it tells us that whilst using the mean familial age at onset as a predictor for the age at onset in *MAPT* mutations provides an adequate estimate, it does not do so for *GRN* and *C9orf72* mutations, and better markers of staging during the presymptomatic period will be required.

Potential Outcome Measures for Genetic Frontotemporal Dementia Trials

Much work has been undertaken to understand the pattern of changes occurring in the natural history of genetic FTD, and most recently, this has been mainly through the observational cohort studies that form part of the FPI [2, 7, 19].

Clinical

Few well-validated clinical scales have been developed in genetic FTD. The most well studied is the Clinical Dementia Rating scale plus National Alzheimer Coordinating Center Frontotemporal Lobar Degeneration Module (NACC FTLD) module (previously known as the 'FTLD CDR'), which is able to capture early symptoms in genetic FTD [12]. Less work has been done on the Frontotemporal dementia Rating Scale (FRS), but this also has potential use in trials.

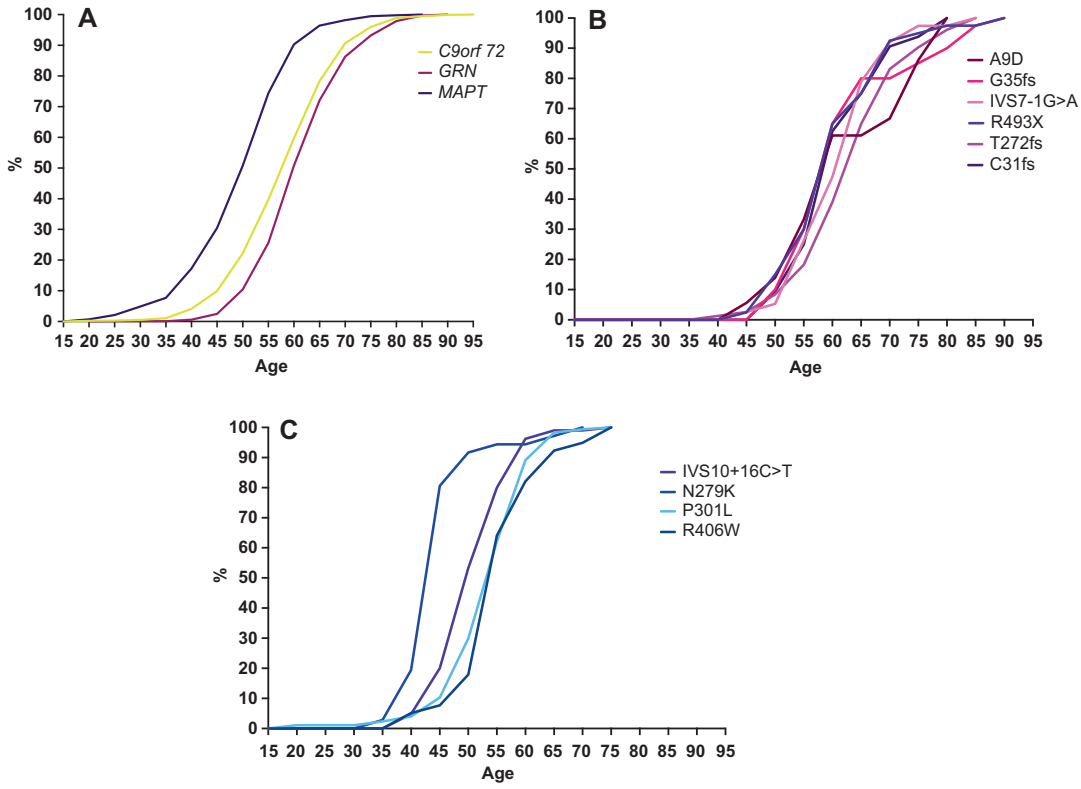

Fig. 1 Range of ages at onset for (**a**) C9orf72, GRN and MAPT mutations overall, (**b**) common GRN mutations and (**c**) common MAPT mutations. (Adapted from Moore et al., Lancet Neurology [13])

Cognitive

Individual neuropsychometric tests have been studied in genetic FTD, with the most sensitive showing change around 5 years before symptom onset [17, 20]. Work is underway to look at cognitive composites, and to look at more novel ways of testing cognition, such as with computerized batteries, wearables and eye tracking.

Magnetic Resonance Imaging

Structural T1 imaging has been the most well studied form of neuroimaging in FTD. Grey matter atrophy occurs at least 10 years before symptom onset in genetic FTD, and probably earlier than this in *C9orf72* mutation carriers [14, 17]. The pattern of atrophy differs across the genetic groups, with early thalamic involvement in *C9orf72* mutation carriers; temporal lobe, particularly medial atrophy early in the disease process in *MAPT* mutation carriers; and insula, frontal and parietal cortical atrophy in *GRN* mutation carriers.

Rates of atrophy are fastest in *GRN* mutation carriers and slowest as a group in *MAPT* mutation carriers, although there is wider variability in the *C9orf72* groups with both fast and slow progressors seen [3, 4].

Use of both whole-brain atrophy rate and specific regions of interest (ROI) atrophy rate (lobar and subcortical structures) are likely to be important in clinical trials, but with more work to be done on identifying the most robust post-processing methodology that leads to the lowest sample size calculations, and the best ROIs to be used in the different genetic groups.

T2 imaging reveals the presence of white matter hyperintensities in *GRN* mutation carriers. However, a recent GENFI study revealed their

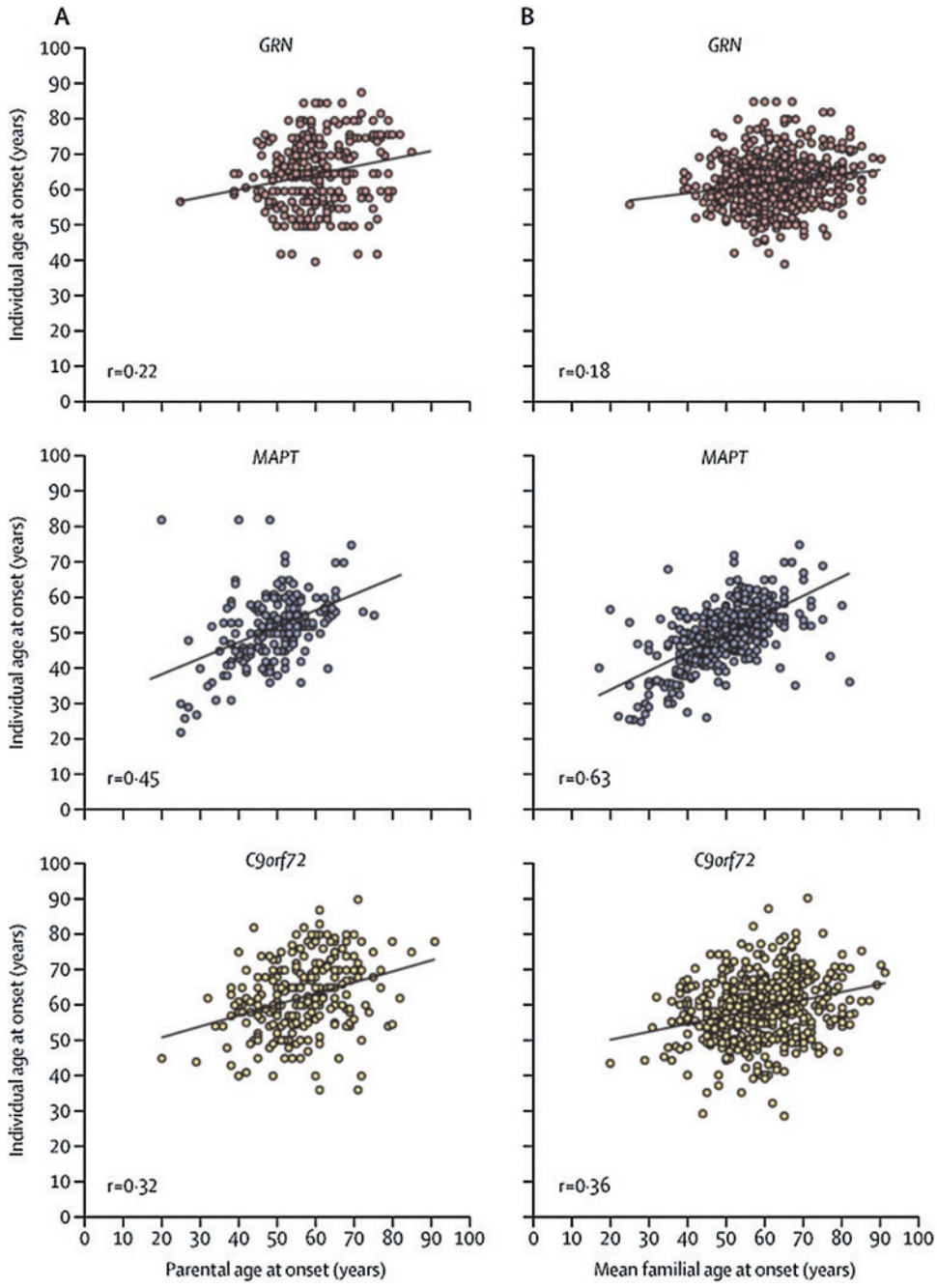

Fig. 2 Correlation of individual age at onset with parental (**a**) and mean familial (**b**) ages at onset. (From Moore et al., Lancet Neurology [13])

presence in only a subset of cases [21], for example, in the symptomatic *GRN* group, 25.0% had none/mild white matter hyperintensity (WMH) load, 37.5% had medium and 37.5% had a severe load. This makes the use of WMH measurement difficult in trials across the entirety of a *GRN* cohort.

Diffusion tensor imaging (DTI) reveals impaired structural connectivity preceding grey matter atrophy [9], and this opens up the opportunity for earlier measurement of change in genetic FTD. However, little work has been performed longitudinally in DTI in genetic FTD, and DTI is more prone to multicentre, cross-scanner issues than T1 imaging, which potentially limits its use in trials.

Other MR imaging modalities such as functional MRI and arterial spin labelling MRI remain poorly studied in genetic FTD, with limited understanding of the variability, extent of longitudinal change and robustness to measurement across multiple scanners within a trial setting.

Positron Emission Tomography Imaging

Relatively less work has been performed in PET imaging than in MRI in FTD. However, hypometabolism using 18F-FDG-PET is also seen up to 10 years prior to symptom onset, although patterns are less clear across the genetic groups than for atrophy using structural imaging.

Whilst the tau PET ligand flortaucipir binds well to the paired helical filament–type tau seen in V337M and R406W *MAPT* mutations, it binds less well to the other forms of tau seen in other *MAPT* mutations [22], and so is not at a stage where it could be adequately used in trials of *MAPT*-related FTD.

Novel tracers are under investigation, including those identifying inflammation, synaptic abnormalities and mitochondrial dysfunction, but these remain some time away from being usable as outcome measures.

Fluid Biomarkers

Two key disease-specific markers are likely to be important outcome measures for genetic FTD trials:

1. Serum, plasma and cerebrospinal fluid (CSF) progranulin have excellent sensitivity and specificity for detecting pathogenic *GRN* mutations [6], with levels low from a young age, and relatively stable over time. Levels are approximately half of 'normal' progranulin levels, and the majority of therapies aimed at *GRN*-related FTD will be aiming to normalize levels by (at least) doubling progranulin measured in biofluids. There is some variability in the different commercially available progranulin assays, and work in the FPI is currently underway to understand that better.
2. Increased CSF poly(GP) levels are seen in both presymptomatic and symptomatic *C9orf72* expansion carriers [11]. Although not felt to be the toxic dipeptide repeat species, poly(GP) levels are currently the best markers available that appear to be a direct surrogate of the pathology seen in *C9orf72*-related FTD, and disease-modifying therapies would be expected to reduce the levels back to 'normal' (essentially zero). However, with current assays, some mutation carriers have very low levels, overlapping with controls. Newer, more sensitive, assays will therefore be required for trials that more clearly separate controls and carriers.

Two other markers have clear potential for use in trials:

1. Neurofilament light chain (NfL, either in CSF or blood) is a measure of disease intensity in FTD, and it predicts progression and survival. Levels increase just prior to symptom onset and appear to continue to increase during the symptomatic period, at least in *GRN* mutations [10, 23].
2. Glial fibrillary acidic protein (GFAP) appears to also increase just before symptom onset in *GRN*-associated FTD [8], although more work is needed to understand longitudinal change in this marker.

More speculatively, markers, such as YKL-40 and chitotriosidase, may index an inflammatory process that occurs in genetic FTD, particularly in *GRN* mutation carriers, although more work is

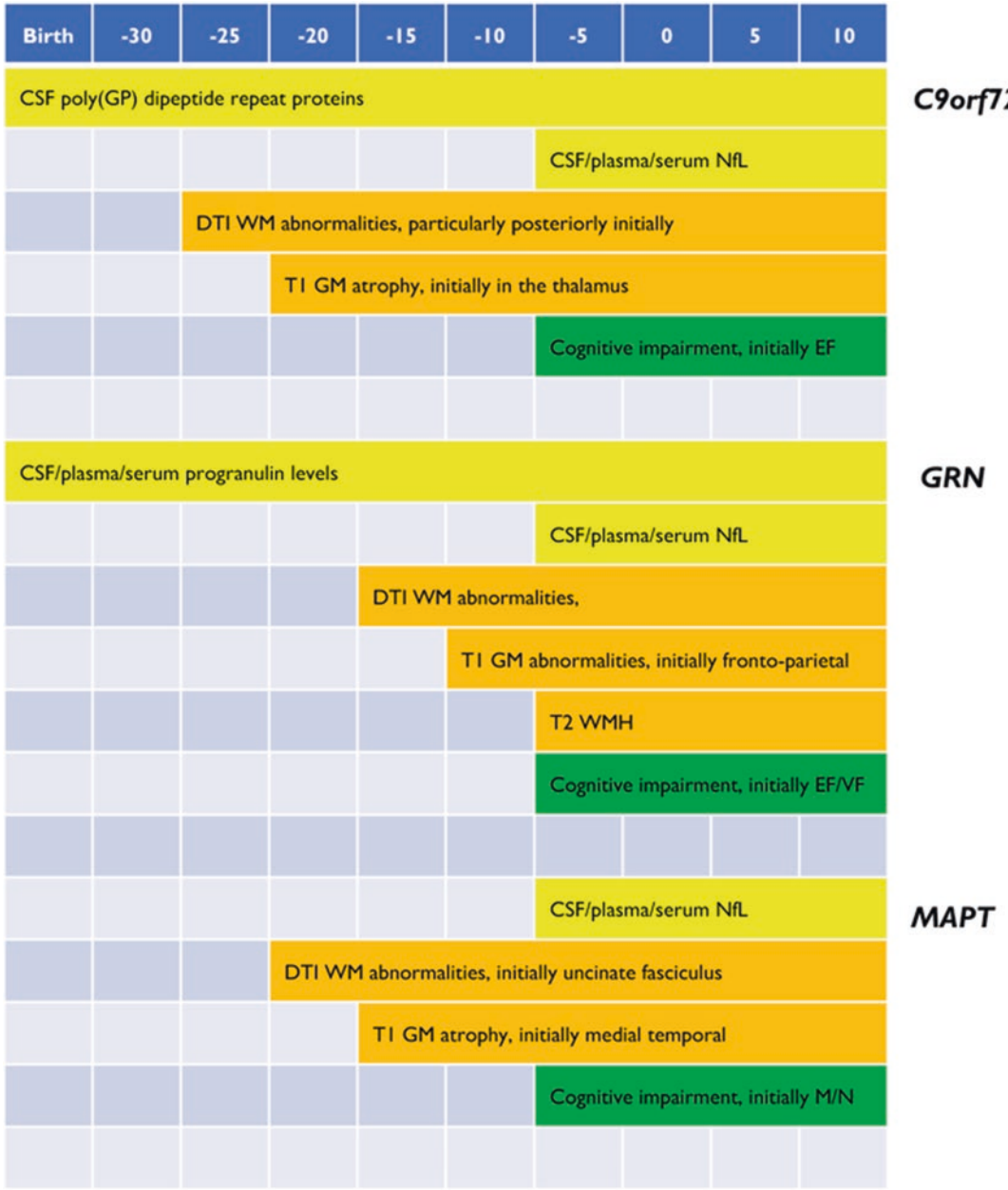

Fig. 3 Schematic of cognitive (green), imaging (orange) and fluid (yellow) biomarker profiles across the lifespan of C9orf72, GRN and MAPT mutation carriers. (From Greaves et al. [7])

needed in this field, as well as in the field of lysosomal and synaptic measures.

A summary of the key biomarker changes that occur through the timeline of the different genetic forms of FTD is shown in Fig. 3. A strategy employed in other rare neurological disorders to improve power to detect treatment effects and better estimate time of disease onset is the construction of Bayesian disease progression models based on multimodal data such as those mentioned earlier [16]. The Dominantly Inherited Alzheimer's Network Treatment Unit (DIAN-TU)

has used such a model as the basis for their adaptive clinical trial platform, allowing for streamlined testing of potentially disease-modifying agents for the prevention of genetic Alzheimer's disease [1].

Current and Planned Trials in Genetic Frontotemporal Dementia

The FPI is currently collaborating with a number of pharmaceutical companies on clinical trials for genetic FTD:

1. **Alector** (https://alector.com) is currently undertaking a phase 2 trial for *GRN* mutation carriers at centres within the FPI (and is about to start its phase 3), with a monoclonal antibody against sortilin. Early data suggest the ability of the drug to increase progranulin levels back into the normal range.
2. **Ionis Pharmaceuticals** (https://www.ionispharma.com) in partnership with **Biogen** (https://www.biogen.com) have developed antisense oligonucleotide (ASO) therapies for MAPT and C9orf72, which are currently being tested in Alzheimer's disease and *C9orf72*-related ALS respectively.
3. **Prevail Therapeutics** (https://www.prevailtherapeutics.com) and **Passage Bio** (https://www.passagebio.com) are developing Adeno-Associated Virus gene therapy for *GRN* mutation carriers.
4. **Wave Life Sciences** (https://www.wavelifesciences.com) is developing an ASO therapy for *C9orf72* mutation carriers.
5. **Arkuda** (https://www.arkudatx.com) is developing a therapy for *GRN* mutation carriers.

The Future

We hope to create an international collaborative group of academic FTD research centres, patient advocacy groups and research foundations that are dedicated to finding a cure for genetic FTD. Through this group, we hope to be a voice for genetic FTD family members, working to design and run the best possible clinical trials. Whilst there remains much work to be done, we have come a long way from single-centre observational studies of small numbers of mutation carriers, to a collaborative group of large-scale cohort studies, entering a new era of clinical trials of potentially disease-modifying therapies and a hopefully different future for genetic FTD.

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Fluid Biomarkers of Frontotemporal Lobar Degeneration

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Introduction

The improved understanding of frontotemporal dementia (FTD) coupled with the emergence of clinical trials has generated much interest in identifying fluid biomarkers that reflect FTD pathophysiology. Generally speaking, a biomarker is a measurable indicator of a normal biological or pathological process. There are currently no FTD-specific fluid biomarkers routinely used in clinical practice. Diagnosing FTD on clinical grounds alone is frequently challenging, especially in the early stages of the disease. A correct and timely diagnosis is needed for appropriate management and support and to exclude treatable causes. At the same time, disease-modifying drugs may be most effective if administered at an early stage, i.e., when neuronal damage is minimal [1]. A biomarker that can identify early disease stages could therefore not only improve clinical management but also have a key position in participant selection for clinical trials. In light of the relative difficulty of quantifying short-term changes in cognitive functioning or atrophy rates, such biomarkers might also be useful as surrogate markers of treatment effect.

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Pathologically, FTD is characterized by frontotemporal lobar degeneration (FTLD) with intracellular inclusions, which are most commonly composed of the microtubule-associated protein tau (FTLD-tau) or TAR-DNA-binding protein-43 (TDP-43; FTLD-TDP). Less common forms include FTLD-FUS (inclusions composed of the FUS protein) and FTLD-UPS (ubiquitin-positive inclusions without immunoreactivity for TDP-43 or FUS) [1, 2]. While the underlying neuropathology is known in genetic forms of FTD, with *MAPT* mutations leading to FTLD-tau and *GRN* and *C9orf72* mutations leading to FTLD-TDP, it is not easily predicted in sporadic FTD based on clinical presentation alone [1]. Fluid biomarkers that can help to identify the pathological substrate will be critical to select patients for etiology-directed therapeutic trials.

This chapter explores the current state of fluid biomarkers in sporadic and genetic FTD and discusses challenges in novel fluid biomarker development.

Fluid Biomarker Sources

Cerebrospinal Fluid

Cerebrospinal fluid (CSF) has gathered the most interest as a source of fluid biomarkers in neurodegenerative diseases. Its proximity to the brain and direct connection with the brain inter-

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stitial fluid means that it is most likely to contain brain-derived proteins related to neurological disease. CSF can be obtained through a lumbar puncture, a safe procedure with post-lumbar puncture headache being the most significant complication, occurring in approximately 10% of patients [3]. However, lumbar puncture is invasive and inconvenient for monitoring disease progression, and variability in the methods used to collect and store CSF can considerably affect the measurement of certain analytes [4].

Blood

Blood is an attractive alternative to CSF as its collection is minimally invasive and therefore more suitable for repeated collection and disease monitoring. A small fraction of brain proteins that cross the blood–brain barrier can be detected in very low concentrations in the blood [5]. Recent technical developments in the field of ultrasensitive assays and mass spectrometry have greatly improved the detection of these brain-derived proteins [6]. Blood biomarker development poses several challenges, including the possibility that the measured analyte is derived from peripheral tissues instead of the brain, interference with immunoassay platforms by resident blood proteins (albumin, immunoglobulins), and potential degradation or masking of pathological markers through protease or protein carrier activity [5, 7].

Other Biomarker Sources

There is a growing interest in biomarkers in other non-invasively obtained biofluids, including saliva and urine. Several studies have shown that amyloid-β peptides and multiple tau species are detectable in saliva, although results in patients with neurodegenerative diseases are conflicting and require replication [5, 8]. While promising, these biomarkers require considerable work to determine their clinical utility and are not discussed further here.

Amyloid-β and Tau

Background

The CSF biomarkers amyloid-β_{42} ($A\beta_{42}$), phosphorylated tau_{181} ($p\text{-}tau_{181}$), and total tau (t-tau) are increasingly being used in clinical practice to detect Alzheimer's disease (AD) and are thought to directly reflect hallmark pathological changes of AD, namely, cortical amyloid plaques, neurofibrillary tangles, and neuronal loss [9]. Amyloid plaques are extracellular aggregates of Aβ peptides which are formed after sequential cleavage of amyloid precursor protein (APP). While most Aβ peptides are 40 amino acids in length ($A\beta_{40}$), the larger $A\beta_{42}$ is considered more toxic due to its greater tendency to aggregate and misfold [10, 11]. Neurofibrillary tangles are cytoplasmic aggregates of hyperphosphorylated tau protein and are thought to be neurotoxic [9].

Patients with AD typically have reduced CSF levels of $A\beta_{42}$, due to cortical amyloid deposition, coupled with increased $p\text{-}tau_{181}$ due to tangle formation, and increased total tau, which is attributed to neuronal loss [12–16]. Together, these findings constitute the so-called AD CSF profile, which provides good diagnostic accuracy to identify patients with AD [17] and has recently been incorporated into research diagnostic criteria [12]. Levels of these CSF biomarkers have been shown to correlate with pathological load on post-mortem examination [13, 15, 16, 18]. Of note, these biomarkers can already detect AD pathology in preclinical and prodromal disease stages, and can be used to predict incipient AD in patients with mild cognitive impairment [17, 19].

CSF Amyloid-β and Tau in FTD Diagnosis

In FTD, $A\beta_{42}$ and $p\text{-}tau_{181}$ are typically normal and t-tau levels may be normal or elevated, likely due to a release of tau protein following neuronal loss [20–22]. Thus, in the diagnostic workup of FTD, these biomarkers are useful to exclude underlying AD, but cannot confirm or rule out FTD pathology. An elevated ratio of $p\text{-}tau_{181}$:$A\beta_{42}$

or t-tau:$A\beta_{42}$ provides an especially accurate differentiation of FTD from AD (sensitivity 87–89%, specificity 79–80%) [23]. This may be particularly relevant in patients with inconclusive clinical presentations, such as prominent behavioral symptoms, which can be ascribed to behavioral variant FTD or frontal variant AD, or primary progressive aphasia, which can be a feature of either FTD or AD [24]. Correctly identifying patients with underlying AD has become increasingly important with the advent of cholinesterase inhibitors and memantine, which are effective in reducing symptoms in AD but not in FTD and may even worsen FTD symptoms [25, 26].

Remarkably, lower levels of the secreted form of APP (sAPPβ) have been reported in FTD patients compared to both AD patients and cognitively healthy subjects, [27–29] suggesting that APP-derived peptides may be involved in FTD through amyloid-independent mechanisms.

Potential Pitfalls of CSF Amyloid-β and Tau

Importantly, postmortem studies have revealed that FTD patients frequently have some degree of concomitant AD pathology [30]. Especially in patients over the age of 75 years, some degree of AD pathology is common, and up to 30% of cognitively healthy elderly subjects have an AD CSF profile [31, 32]. Therefore, in patients with an AD CSF profile who are clinically suspected of having FTD, the possibility of AD and FTD copathology should be considered.

Furthermore, between-individual variation in overall Aβ production or secretion may cause $A\beta_{42}$ to fall within the normal range despite underlying amyloid pathology; the use of $A\beta_{42/40}$ ratios is thought to provide a more reliable measure [33].

CSF Aβ and tau measurements are sensitive to variations in (pre)analytical conditions. Recommendations for optimal CSF collection include the use of polypropylene collection tubes since $A\beta_{42}$ and other proteins adhere to polystyrene tubes, significantly reducing measured concentrations; similarly, the use of lumbar catheters or manometers should be avoided [4]. Variability also exists between and within commercially available ELISA-based assays, calibration peptides, and platforms, meaning that interlaboratory and interassay consistency is poor, [34] and direct comparisons between laboratories and techniques are not reliable [18]. International efforts are underway to harmonize protocols and assays within and between laboratories [35].

CSF Tau to Differentiate Between Pathological Subtypes of FTD

Two previous studies did not find a difference in CSF p-tau_{181} between FTD patients with or without underlying tau pathology, [36, 37] although one study did reveal an association between the severity of tau pathology and CSF p-tau_{181} levels in FTD patients [38]. The ratio of p-tau_{181} to t-tau is lower in patients with FTLD-TDP than in those with FTLD-tau, [1, 39–42] although this finding may be driven by the presence of concomitant amyotrophic lateral sclerosis (ALS) (leading to more pronounced neuronal loss and thus higher t-tau levels) in some patients with FTLD-TDP. Novel tau fragments to distinguish FTLD-tau from FTLD-TDP pathology have thus far yielded insufficient diagnostic accuracy [18, 43].

Blood Amyloid-β and Tau

There is a growing interest in the measurement of Aβ and tau species in blood as an alternative to CSF. Although previous results were conflicting, recent studies using ultrasensitive analytical assays have demonstrated decreased levels of blood $A\beta_{42}$ in patients with AD. Blood and CSF $A\beta_{42}$ levels are correlated and blood $A\beta_{42}$ appears to reflect AD-associated pathology with a fair diagnostic accuracy [44, 45]. Similarly, plasma tau levels are increased in AD patients compared to controls, although not as clearly as in CSF, hampering its diagnostic use [44, 45]. These results are promising and warrant further research in larger cohorts.

Neurofilament Proteins

Neurofilament proteins (Nfs) are rapidly emerging as the most promising fluid biomarkers for FTD [46]. The discovery that an elevation of neurofilament light chain (NfL), which is thought to reflect neuroaxonal damage, can be measured reliably both in CSF and blood has created much interest in NfL as an easily accessible biomarker across a spectrum of neurological diseases [47, 48].

Background

Nfs are cylindrical heteropolymers located exclusively in the neuronal cytoplasm and are the dominant protein of the axonal cytoskeleton. Nfs consist of three subunits, classified according to molecular weight: neurofilament light chain (NfL), medium chain (NfM), and heavy chain (NfH). Nfs are thought to be critical for stability and radial growth of axons, thereby modulating nerve conduction velocity [49]. Under normal circumstances, Nfs are stable within axons and have a low turnover rate. Upon damage to the axon, Nf molecules are released into the extracellular space, where they traffic to the CSF and, after passing through the blood–brain barrier, enter the bloodstream [49, 50]. The release of Nfs occurs irrespective of the etiology of the neuroaxonal injury; therefore, elevated levels are seen in CSF and blood in patients with various neurological disorders, including dementia, stroke, traumatic brain injury, multiple sclerosis, and Parkinson's disease [47, 48]. Due to its relative abundance and solubility, NfL can be more readily quantified in biofluids than NfH and NfM [49]. Blood and CSF NfL levels are highly correlated [51–53] and advances in ultrasensitive assays (single molecule array, Simoa) have greatly improved the accuracy of blood NfL measurements [54].

Neurofilament Light Chain in FTD

A large number of studies have consistently reported strongly elevated NfL levels in CSF and blood of FTD patients, with a diagnostic accuracy of over 90% to distinguish FTD patients from healthy individuals [55, 56]. These NfL increases occur in all FTD phenotypes, [28, 57–63] with especially high levels in patients with concomitant ALS [52, 60, 64, 65]. Although higher levels have been reported in patients with FTLD-TDP compared to those with FTLD-tau, this difference may be driven by patients with concomitant ALS in the FTLD-TDP group [41, 58, 65, 66].

NfL levels are significantly higher in FTD than in other frequent causes of dementia, including AD, vascular dementia, and dementia with Lewy bodies [55, 62, 64, 67, 68]. The pronounced NfL elevations seen in FTD may be related to the anatomical location of neurodegeneration or due to a higher rate of neuronal death, since especially high NfL levels are also seen in the rapidly progressive Creutzfeldt-Jakob disease [66, 69]. However, considerable overlap in NfL levels exists between dementias, and the discriminatory power of NfL on its own to distinguish FTD from disease mimics is only modest [55]. A promising strategy may be to combine NfL with other fluid biomarkers; for instance, the addition of NfL to core AD CSF biomarkers significantly improves the discrimination between AD and FTD compared to AD CSF biomarkers alone [66, 67].

NfL appears to be a useful diagnostic biomarker to distinguish FTD from non-neurological disorders, including primary psychiatric disorders, in which NfL levels are typically normal [70–73]. Blood NfL may provide an easily accessible, inexpensive screening tool to identify patients who are likely to have an underlying neurological disease and require further investigation.

Importantly, patients with high NfL levels have more brain atrophy, more functional and cognitive impairment, faster disease progression, and shorter overall survival than patients with low NfL levels, [52, 61, 62, 65, 66, 68, 74, 75] demonstrating the value of NfL as a prognostic biomarker. NfL may therefore be a useful tool to inform patients and caregivers about the expected clinical course, and to distinguish patients with clinical hallmarks of FTD who are likely to further decline from those with non-

progressing variants (benign or phenocopy FTD syndrome) [76].

Presymptomatic carriers of mutations in *GRN, C9orf72,* and *MAPT* typically have low NfL levels, [52, 60, 65] indicating a low rate of axonal turnover, with sharp increases observed at least 1–2 years prior to symptom onset in one longitudinal study [65]. These increases likely reflect early axonal damage in a prodromal disease stage and suggest that NfL could be a valuable selection tool in clinical trials to identify mutation carriers approaching symptom onset. Another promising application of NfL is as a surrogate marker of treatment effect in clinical trials. In multiple sclerosis, NfL decreases have been observed after treatment with anti-inflammatory drugs, [77] and in AD mouse models, NfL decreased after inhibition of amyloid-β production, [78] suggesting that NfL is a dynamic marker of disease activity. As blood NfL levels are generally stable over the course of FTD, [62, 65] a decrease in blood NfL during an FTD trial might reflect a reduced rate of neuroaxonal breakdown in response to the study drug.

CSF and blood NfL levels increase with age among healthy adults, possibly reflecting slow, ongoing axonal turnover as part of physiological aging [47, 48]. This necessitates the development of age-adjusted normal values before NfL can be used in clinical practice. International efforts are underway to harmonize preanalytical and analytical parameters and to develop universal reference values, which will allow a reliable comparison of results from different laboratories [47].

TDP-43

Background

Aggregation of TDP-43 is a hallmark pathological feature of most tau-negative cases of FTD as well as almost all cases of ALS [79–83]. Under normal circumstances, TDP-43 is predominantly localized in the nucleus, [84] where it functions as a transcription factor and regulates important cellular functions such as splicing activity and mRNA stability [85]. In disease, pathological TDP-43 isoforms (phosphorylated and ubiquitinated full-length TDP-43 as well as C-terminal TDP-43 fragments) are redistributed to the cytoplasm, where they form aggregates which are thought to be toxic [79, 82].

Biomarkers of TDP-43 Pathology

Underlying TDP-43 pathology can be predicted in patients with a mutation in *GRN* or *C9orf72*, but not in patients with sporadic FTD [2]. Etiology-specific treatment trials will require biomarkers that can detect TDP-43 pathology during the patients' lifetime to select suitable patients. Thus far, efforts to measure disease-specific forms of TDP-43 in biofluids of ALS and FTD patients have yielded inconsistent results.

TDP-43 antibodies used to date have the ability to detect full-length TDP-43 as well as phosphorylated full-length TDP-43 and longer C-terminal fragments, but not the shorter C-terminal fragments, which are abundant in brain tissue of ALS and FTD patients [86]. Elevated levels of full-length TDP-43 in CSF of patients with ALS or FTD have been reported, [87–89] albeit with considerable overlap between groups, while another study reported decreased CSF TDP-43 in FTD patients [42]. Phosphorylated TDP-43 in CSF was not different in FTD or ALS compared to controls [42, 90]. One small study reported elevated plasma phosphorylated TDP-43 levels in *C9orf72*- or *GRN*-associated FTD; [90] this finding requires replication in larger cohorts.

Accurate quantification of TDP-43 in CSF or blood is challenging for several reasons. TDP-43 is a ubiquitously expressed protein and is abundant under normal circumstances. The majority of CSF TDP-43 appears to be blood-derived and not brain-derived, although it may be possible to enrich for brain-specific fractions of TDP-43 from exosomes in CSF [91]. Monoclonal antibodies which selectively recognize pathological forms of TDP-43, such as short C-terminal TDP-43 fragments, will therefore be critical [86]. Furthermore, quantification of TDP-43 and especially its phosphorylated

form appears limited by very low concentrations or low binding affinity of the antibodies in the presence of abundant immunoglobins or albumin, [92, 93] highlighting the need for technical improvements in assays [83].

Markers of Inflammation and Astrogliosis

Background

Increasing clinical, genetic, and cellular evidence suggests that chronic neuroinflammation plays an important role in FTD. Key observations include microglial and astrocytic activation in the frontal and temporal cortices in both postmortem brain tissue and positron-emission tomography (PET), a shared genetic risk between FTD and autoimmune diseases, and a direct link between several FTD-related genes and inflammatory pathways [94–102]. While the exact contribution and timing of neuroinflammation in FTD remains controversial, different disease stages may be characterized by different immune mechanisms, making neuroinflammation an interesting source for potential fluid biomarkers.

Glial Markers

Microglia, the resident macrophages of the central nervous system (CNS), likely play a central role in neuroinflammation. Resting microglia are involved in homeostasis, and can become activated upon exposure to pathogens or inflammatory stimuli to produce a range of signal molecules, including cytokines, chemokines, and complement molecules, which ultimately result in a pro- or an anti-inflammatory CNS microenvironment [102–105]. Similarly, astrocytes are believed to modulate neuroinflammation [102]. The upregulation of microglia and astrocytes in FTD brains has generated interest in biomarkers that can track glial activation in vivo. Candidate glial biomarkers include YKL-40, chitotriosidase-1 (CHIT-1), and glial fibrillary acidic protein (GFAP).

YKL-40, also known as chitinase 3-like protein 1, is produced primarily by reactive astrocytes but also microglia [106]. CSF YKL-40 is elevated in FTD as well as several other dementias, with especially high levels in aggressive and rapidly progressive dementias [27, 28, 107–113]. Although YKL-40 is thought to be a nonspecific biomarker of glial activation, a positive association has been found with tau deposits, suggesting that YKL-40 upregulation may be particularly sensitive to tau aggregation [27].

CHIT-1 is an enzyme which is expressed and secreted by activated microglia. A recent study in 72 FTD patients reported elevated CHIT-1 levels compared to controls, [114] although a previous smaller study did not find these elevations [115]. Importantly, CHIT-1 concentration may be reduced in subjects carrying a *CHIT1* polymorphism common in European populations, complicating its use as a biomarker [115, 116].

GFAP, a cytoskeletal filament protein in astrocytes, is produced and released by astrocytes during neurodegeneration [117]. High levels of GFAP in blood have been found in several neurodegenerative diseases, with remarkably high levels in FTD, [118, 119] suggesting that astrogliosis may be an especially prominent feature of FTD.

The microglial transmembrane receptor TREM2 appears to play a role in microglial homeostatic pathways, [120] and has been investigated as a candidate biomarker for neurodegeneration since genetic variants of *TREM2* are associated with an increased risk of FTD, AD, ALS, and Parkinson's disease [121–126]. Its ectodomain can be released into the extracellular space as a soluble protein (sTREM2), which is measurable in CSF and blood [127]. While small studies reported conflicting results in sTREM2 levels [128–130], a more recent larger study observed no differences between FTD patients versus controls except in a small number of *GRN* mutation carriers [131].

While these glial markers provide further evidence for aberrant microglial and astrocytic activity in FTD, their diagnostic potential is limited, as considerable overlap exists with controls. Similarly elevated levels have been reported in several other neurodegenerative diseases, likely

reflecting a shared, nonspecific glial activation. Furthermore, YKL-40, CHIT-1, and TREM2 are expressed by multiple peripheral cell types, which could affect their measurement [107, 120, 132]. GFAP, on the other hand, is brain-specific and therefore may be a more interesting candidate [117].

Cytokine Markers

There is extensive, although somewhat conflicting, evidence for altered pro- and anti-inflammatory cytokine profiles in CSF and blood [102]. For instance, increased levels of blood interleukin-6 (IL-6) were found in *GRN* mutation carriers [133] and sporadic FTD, [134] whereas another study showed no differences in CSF IL-6 in FTD versus controls [135]. Tumor necrosis factor α (TNF-α) was increased in CSF of patients with sporadic FTD, [136] while another study showed a reduction in 10 *GRN* mutation carriers [137]. More consistently elevated levels have been found for monocyte chemoattractant protein 1(MCP-1) [137–139].

These results are mostly derived from small studies and must be interpreted with caution. Peripheral cytokine measurements may be influenced by concurrent infections or other inflammatory conditions outside of the brain. Furthermore, cytokine profiles likely vary depending on the disease stage. Finally, the interpretation of increased or decreased cytokine levels is complex: the original classification of pro-inflammatory and anti-inflammatory cytokines is likely too simplistic, as a given cytokine may behave as either pro- or anti-inflammatory depending on the circumstances [140].

Other Candidate Biomarkers of Neuroinflammation

One study of patients with *GRN*-associated FTD has demonstrated increased CSF levels of the complement proteins C1q and C3b [141]. C1q and C3b are essential components of the classical and alternative complement pathways, which comprise a sequence of protein cleavages and eventually contribute to a pro-inflammatory state. Mouse models have suggested a role for complement proteins in the breakdown of synapses, an early neurodegenerative process, underlining the need for replication of complement protein measurements in CSF and blood [141].

Gene-Specific Biomarkers

Progranulin in GRN Mutation Carriers

Background

Progranulin (PGRN) is a ubiquitously expressed growth factor, which plays important roles in normal tissue development, cell proliferation and regeneration, and inflammation. In the brain, PGRN is expressed in neurons and microglia and promotes neurite outgrowth, neuronal survival, and differentiation, although its exact physiological roles in the nervous system are not fully understood [142]. PGRN also appears to suppress neuroinflammation and modulate neuronal lysosome function, with homozygous mutations in *GRN*, the gene encoding PGRN, leading to the lysosomal storage disease neuronal ceroid lipofuscinosis [143]. PGRN can be cleaved into granulins, which are also biologically active, but often with opposing actions, suggesting that the equilibrium between PGRN and granulins is important for tissue homeostasis [142].

Progranulin in FTD

Heterozygous mutations in *GRN* are among the most common causes of genetic FTD [144–146]. Most pathogenic *GRN* mutations introduce a premature stop codon that triggers nonsense-mediated decay of *GRN* mRNA, leading to a 50% reduction of PGRN protein levels through haploinsufficiency [144, 145]. This reduction in PGRN levels can be detected through immunoassays both in the CSF and blood, enabling accurate recognition of FTD patients due to a *GRN* mutation versus those with sporadic FTD (sensitivity 96%, specificity up to 100%) [147 –154]. PGRN levels are already decreased in the presymptomatic stage, even in the second or third

decade of life, indicating that dysregulated PGRN expression is a very early event during the lifespan of mutation carriers. Blood PGRN levels can therefore also distinguish presymptomatic *GRN* mutation carriers from noncarriers with near-perfect sensitivity and specificity [150, 155]. Its concentration does not reflect the extent of neurodegeneration and is therefore not useful as a prognostic or disease staging biomarker [150].

Blood PGRN measurements may be helpful to determine the pathogenicity of novel *GRN* mutations or to detect mutations not found on standard genetic screening, such as large deletions [150]. Since genetic testing is expensive and time-consuming, blood PGRN determination offers a low-cost, minimally invasive screening tool to identify *GRN* mutation carriers, who should then be subjected to further genetic testing. The ability to screen FTD patients for *GRN* mutations on a large scale is particularly important in light of therapeutic trials aimed at increasing PGRN protein levels [150].

Since blood PGRN appears to be stable over time, [150, 155] PGRN levels can be used to monitor whether a trial drug is effective in increasing PGRN levels. It is important to note that CSF and blood PGRN are only moderately correlated, implying a differential regulation of the two [155–157]. Peripheral PGRN levels may not adequately reflect those in the CNS, and the absence of an effect on blood PGRN does not rule out an effect on the brain or PGRN function. Furthermore, the extracellular PGRN levels measured in biofluids might not sufficiently reflect intracellular levels, and it is not clear yet where the loss of PGRN has its main effect [142].

Much variability in PGRN levels exists within individuals, and various genetic and environmental regulators influence PGRN levels. For example, PGRN levels are elevated in inflammation and other clinical conditions including cancer and pregnancy, [158, 159] and certain single nucleotide polymorphisms (SNPs) are associated with increased or decreased PGRN levels, including rs5848 (*GRN*), rs646776 (*SORT1*), and rs1990622 (*TMEM106B*) [155, 156, 160–162]. Further research is needed to elucidate other factors that may confound PGRN measurements. Given the distinct biological properties of granulin peptides, developing antibodies against granulins to study ratios of PGRN to granulins as potential biomarkers could be insightful [149, 142].

Dipeptide Repeat Proteins in C9orf72 Mutation Carriers

Background

The *C9orf72* repeat expansion is the most frequent genetic cause of FTD and ALS [163–168]. While the exact mechanism by which *C9orf72* repeat expansions lead to neurodegeneration is unknown, it has been proposed that toxic dipeptide repeat proteins (DPRs) could play a role [169]. The expanded *C9orf72* repeats are bidirectionally transcribed into repetitive RNA, which forms sense and antisense RNA foci. These RNAs can be translated in every reading frame through repeat-associated non-ATG-initiated translation (RAN translation), generating five DPRs, in order of abundance: poly(GA), poly(GP), poly(GR), poly(PA), and poly(PR) [170]. DPRs are found abundantly in brains of *C9orf72*-FTD/ALS patients, [170–173] mostly in cytoplasmic neuronal inclusions, although DPR burden does not coincide neuropathologically with the degree of neurodegeneration [174–177]. Cell and animal models have shown that poly(GR) and poly(PR), and to a lesser extent poly(GA), are toxic when overexpressed, while poly(PA) and poly(GP) are unlikely to be toxic [169].

Dipeptide Repeat Proteins in CSF

Poly(GP) can be quantitatively detected by ELISAs in CSF, [178] revealing high levels in patients with ALS or FTD due to *C9orf72* repeat expansions. In sporadic cases, on the other hand, poly(GP) levels are generally very low or undetectable, [178, 179] although one study reported high poly(GP) levels in a small number of patients without the repeat expansion [180]. One possible explanation could be somatic mosaicism, where a pathological repeat is present in the CNS but not in peripheral blood, preventing the detection of *C9orf72* repeat expansions in peripheral blood. It has been shown in mice that CSF poly(GP) levels correlate with DPR protein pathology, repeat RNA levels, and RNA foci burden [179].

CSF poly(GP) elevations are already observed in presymptomatic *C9orf72* mutation carriers, [180–182] suggesting that DPR protein production emerges prior to neurodegeneration. This is in agreement with the neuropathological detection of DPRs in young presymptomatic *C9orf72* cases [183–185]. CSF poly(GP) levels do not correlate with the severity of neurodegeneration, disease progression, or other clinical characteristics such as the age of disease onset [179–182], limiting the value of poly(GP) as a disease staging or prognostic biomarker.

Since the RNA transcripts of expanded *C9orf72* repeats are believed to play a key role in *C9orf72* pathogenesis, interventions targeting transcription and translation of the repeat expansion are a promising therapeutic strategy. Poly(GP) levels appear to be stable over time, [179] and therefore measurement of poly(GP) before and during treatment presents a feasible approach to measure target engagement. Antisense oligonucleotides (ASOs) targeting repeat RNAs have been shown in mice to reduce CSF poly(GP) levels [179].

Importantly, poly(GP) can be detected in peripheral blood mononuclear cells (PBMCs); further research is needed to determine its potential as a blood-based biomarker [179].

Most research to date has focused on measuring poly(GP) due to its high abundance and solubility, making it the most likely DPR to be accurately measured [169]. Measurements of poly(GA) and poly(GR) might uncover associations with clinical features not observed for poly(GP). To date, efforts to measure poly(GA) and poly(GR) in CSF have been unsuccessful, possibly because the currently used assays are not sensitive enough to detect very low concentrations of these DPRs [186].

Concluding Remarks and Future Directions

Recent years have seen great advances in identifying both general biomarkers of neurodegeneration, such as NfL, as well as gene-specific biomarkers, including PGRN and DPR proteins. There remains an unmet need for biomarkers that specifically reflect FTD pathophysiology and, especially with the advent of clinical trials, biomarkers that can predict the underlying neuropathological substrate in sporadic FTD.

The heterogeneity of FTD complicates biomarker development, and the use of a clinical diagnosis as a reference standard is a potential source of heterogeneity given the high false-positive rate of FTD clinical diagnosis [30]. Although novel biomarkers would ideally be validated in postmortem studies, studying genetic forms of FTD, in which the underlying pathological substrate can be accurately predicted during life, provides a valuable alternative. A combination of analytes that reflect different biological processes is likely to yield more information than single biomarkers. Longitudinal studies are needed to determine at what stage during the disease various biomarkers start to become abnormal.

The use of proteomics is a promising strategy to detect differentially regulated proteins in biofluids, although in-depth validation of mass spectrometry results is needed to overcome differences in technical parameters [187]. Candidate proteins that have been identified in multiple independent CSF proteomics studies are likely the most promising and include synaptic proteins, such as neuronal pentraxins and VGF, as well as numerous inflammation-related proteins [187–193].

A crucial step before a biomarker can be implemented in clinical practice is multicenter standardization and harmonization of preanalytical and assay characteristics, as is currently being done for core AD biomarkers [35]. Developing normal reference values and cut-points is essential and needs to take into account age-related changes in biomarker levels, such as is the case for NfL and several inflammation-related biomarkers [102]. Many of the biomarkers discussed in this chapter are not FTD-specific (e.g., NfL) or brain-specific (e.g., markers of neuroinflammation, TDP-43), and a thorough understanding of potential confounding factors is needed before these biomarkers can be relied upon in a clinical setting.

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Frontotemporal Dementia: A Cross-Cultural Perspective

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Introduction

Frontotemporal dementia (FTD) is the term used to indicate clinically and pathologically heterogeneous neurodegenerative syndromes, featuring unrelenting decline in temperament, judgment, conduct, and verbal communication. The onset of FTD occurs most frequently in midlife; most commonly the illness is recognized before age 60. However, when the onset occurs earlier, in youth, the symptoms may mimic a primary psychiatric disorder, for example, schizophrenia or bipolar disorder [1]. Cases arising in the seventh decade of life and later have also been reported [2].

The best known FTD phenotypes are defined, according to the profile of disability and dysfunction, by the behavioral changes, the language deficits, or a combination of cognitive and neurological symptoms. The behavioral phenotype, that is, behavioral FTD, is dominated by dissocial behaviors such as indifference, insensitivity, jocularity, impulsiveness, and compulsive behaviors. Two main language phenotypes are recognized, one, non-fluent FTD, characterized by effortful, dysfluent, non-grammatical speech and difficulty understanding sentences; the other, semantic FTD, by fluent speech, with anomia, agnosia for words and objects, and vacuousness. The features of the behavioral and language phenotypes reflect the degeneration of frontal and temporal cortices. One also encounters FTD syndromes characterized by the association of cognitive, behavioral, or language symptoms with motor dysfunctions that reflect early degeneration of subcortical structures; this combination occurs in diseases such as corticobasal degeneration and progressive supranuclear palsy. It is to be noted that whatever the presenting phenotype may be, FTD progresses to a severe dementia [3].

FTD has been recognized in many countries (see Fig. 1). However, the scope of clinical activity and research varies widely across regions, reflecting, in our view, local expertise, local resources, public health priorities, and sociocultural factors. This chapter attempts to provide a perspective about the international FTD landscape, describing, first, the distribution and demographics; second, the clinical and genetic epidemiology; and, lastly, considering how the diversity of geographic and cultural settings impacts diagnosis, care, and research.

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Fig. 1 Geographical distribution of centers active in research and clinical care focused on frontotemporal dementia. Flags indicates the location of individual centers

Worldwide Distribution of Frontotemporal Dementia

In the past three decades, the frequency of FTD has been described in more than 30 population-based studies from around the world—Australia [4], Brazil [5, 6], Canada [7], Finland [8], Germany [9], India [10], Italy [11–15], Japan [16–20], Netherlands [21], Nigeria [22], Spain [23, 24], South Korea [25], Sweden [26, 27], Turkey [28], the United Kingdom [29–33], and the United States [34].

The most recent systematic review, conducted for the period 2000–2012, summarizes data from studies that were carried out in catchment areas geographically located in 15 countries of the American, European, and Asian continents and showed a point prevalence range of 0.01–4.61/1000 persons [35]. Three-point prevalence rates that fall within that range, from Japan [20], Australia [4], and the United Kingdom [33], were not included in the review because they became available after 2012. Several studies conducted in India, Korea, Japan, Sweden, and the United Kingdom, during the period 2000–2012, report 1-year cumulative prevalence rates that range 0.16–2.85 per 1000—excluding that from an outlier (31.04/1000), which used an uncommon case definition and a narrow non-representative age range [27]. A study from Nigeria provides a 10-year cumulative prevalence of 0.01/1000 persons, based on archival data, collected from 1998 to 2007, from a large regional neuropsychiatric hospital [22]. However, in the study, the focus on hospital care and the retrospective ascertainment may have resulted in a lower prevalence of FTD than might be found in the reference population.

The worldwide FTD incidence rate of 0.00–0.33/1000 person-years (see Table 1) was estimated from data deriving from a national registry in Denmark [36], as well as catchment area studies conducted in Brazil, Italy, Spain, the United

Table 1 Incidence of frontotemporal dementia (FTD) worldwide

Study/location	Sampling frame and case ascertainment	Age	Years of study	Incidence[a]	95% CI
Knopman et al., 2004 Rochester, USA	City/suburban area; linked and coded records	40–69	4	0.04	0.02–0.11
Nitrini et al., 2004 Cantadeluva, Brazil	Municipality; assessment and diagnostic conference	65+	3	0.28	0.04–1.96
Ravaglia et al., 2005 Conselice, Italy	Provincial town; assessments and diagnostic conference	65+	5	0.33	0.05–2.33
Mercy et al., 2008 Cambridgeshire, UK	Large borough; assessments and diagnostic conference	45–64	6	0.04	0.02–0.06
Garre-Olmo et al., 2010 Girona, Spain	City; assessments and diagnostic conference	30–64	3	0.05	0.04–0.06
Phung et al., 2010 Denmark	Country; national registry, linked and coded records	40+	34	0.00	0.00–0.00
Coyne-Gilchrist et al., 2016 Cambridgeshire and Norfolk, UK	Two large counties; assessments and diagnostic conference	40+	2	0.02	0.01–0.02

[a]Incidence per 1000 person-years

Kingdom, and the United States [6, 11, 24, 32–34, 36].

As noted in the most recent reviews [35, 37], world prevalence and incidence rates for FTD are low and show wide variation. These variations can be explained on methodological grounds. Population-based studies of FTD and other neurodegenerative diseases are technically challenging, due to the difficulty of case definition and ascertainment, the evolving diagnostic rules, as well as the type of expertise and resources that are required [35, 37–39]. Diagnostic criteria have been refined over the past 40 years. Most recently, these refinements were undertaken to address problems related to requirement of the criteria for a multiplicity of symptoms and the rigidity of the algorithms used to define thresholds for diagnosis, as well as a desire to include a ranking for the level of confidence in the diagnosis [40]. The latest criteria [41, 42] addressed these issues, and the next step would be a characterization of interrater reliability, sensitivity, and specificity. The first study to test the interrater reliability of the criteria for behavioral FTD reported an interrater agreement of 82% [43], and another study, using neuropathological data for reference, reported sensitivity and specificity ranging 82–95% and 85–85%, respectively, depending on the assigned level of diagnostic confidence [44]. Positive and negative predictive values were 80–92% and 91–96%, respectively. These estimates are preliminary, as the samples were small or relied on retrospective clinical data. Larger prospective studies are needed to clarify reliability, sensitivity, and specificity of the diagnostic criteria in different clinical and cultural contexts, and to identify areas for refinement.

It is to be noted that geographic regions are diverse with respect to the prevailing cultural and socioeconomic contexts, aspects of which (e.g., poverty, low literacy, lack of infrastructure, and cultural norms) may constitute barriers for research [39]. These challenges explain the variation in the scope, depth, and methodology of FTD surveillance across studies, and, at least partially, the variation in the prevalence and incidence rates. In exceptional circumstances, geographic differences reflect the presence of communities with high rates of mutation carriers [15] or other susceptibility factors. It is also to be noted that current estimates of prevalence and incidence, while of undoubtedly high value for research and policy, are not yet representative of all geographic regions and ethnic groups. The research has been uneven distributed geographically, and there is low ethnic diversity in the studies. For instance, the North American and European cohorts are over 95% Caucasian [37]. In other words, while valuable knowledge has been gained from studies describing FTD distributions in many regions, there is still much to learn.

Genetic Epidemiology

In the past two decades, investigations of familial and hereditary cohorts of FTD have led to the identification of genetic loci for causal dominant mutations, of which the most important are microtubule-associated protein tau (*MAPT*) [45–47], progranulin (*GRN*) [48, 49], and chromosome 9 open reading frame 72 (*C9orf72*) [50, 51]. Mutations of these genes, together, account for a large majority of hereditary FTD in North America and Europe [52], but there are regional variations in the distribution of these mutations. For example, clustering of *GRN* mutations have been observed in northern Italy [53, 54].

The *C9orf72* mutation has a high frequency in North American and European patients who have familial FTD, amyotrophic lateral sclerosis (ALS), or FTD in association with ALS (FTD-ALS)—though it has also been observed in a small proportion of African American, Hispanic American, and Asian patients [55]. *C9orf72* mutations have been also identified in Greek [56] and Turkish [57] cohorts. All *C9orf72* mutation carriers identified in a worldwide epidemiological study (403 and 588 who had FTD or ALS, respectively) were found to have the Finnish founder haplotype by a genome-wide single-nucleotide polymorphism analysis [55]. This finding, which has been replicated many times, points to a founder origin in Northern Europe [58]. The *C9orf72* mutation has been reported as

a common cause of hereditary FTD and ALS in Brazil [59], but there were no data on the ethnic background of the mutation carriers. *C9orf72* carriers have also been identified among a small number of Han Chinese patients [60]. These Chinese carriers have been shown to have the same risk haplotype identified in the European cohorts, a finding suggesting the possibility of a shared common founder [61].

Familial and hereditary FTDs appear to be rare in Asian populations. An international Asian collaborative study, that analyzed data from India, Indonesia, Japan, Philippines, and Taiwan, found that few patients had a relative with FTD [62]. Although mutations in the *CHCHD10* gene [63] were found in about 8% of the subjects in a Chinese clinic series [64], a subsequent study found very few carriers of the *MAPT*, *GRN*, and *CHCHD10* mutations [65]. A novel *GRN* mutation was identified recently in one of 116 subjects in a cohort from southern India [66]; no other carriers have yet been identified. Other studies show that mutations in *C9orf72*, *GRN*, and *MAPT* are rare in China [67–69], Japan [70], South Korea [71, 72], and India [73, 74]. There are no data from Africa pertaining to familial or hereditary FTD. A few studies have reported data on the frequency of mutation carriers among African American or Hispanic American subjects, for example [55], but the numbers have been too low for subgroup analyses. However, in an analysis of data collected from ten centers in the United States and Europe and two additional ones in Jamaica and Nigeria, the *C9orf72* mutation was found in three of the 65 FTD subjects of African descent [75]. As the mutation carriers were African American, they may also have had the Finnish founder haplotype.

Clinical Aspects

Cultural Influences

Cultural context may exert strong influences on the experience, expression, or recognition of behavioral dysfunctions, including those of neurodegenerative diseases such as FTD. In western India, for example, cases tend to present with a severe syndrome [76] in which impulsive and compulsive features are prominent [77]. On the other hand, a report from western Nigeria describes a presentation characterized by abnormal conduct, executive dysfunction, emotional incontinence, and progressive aphasia [78]; however, more data will be needed in order to determine whether other Nigerian cases have similar features. There has been very little description of FTD syndromes in African Americans or Europeans of African descent. Through the analysis of data from the sample of 65 subjects of African descent, it was reported that the behavioral phenotype was most common, and that half the subjects with semantic FTD had behavioral disorder, prosopagnosia, and right-predominant bilateral anteromedial temporal lobe atrophy [75]. Hallucinations were common, even among the cases with language syndromes. Seven subjects had family history of FTD, and three were carriers of the *C9orf72* mutation. None of the four subjects who had motor neuron disease were carriers of the mutation. It must be stated that the degree to which these observations pertain to patients living in Africa is not yet known.

Data from Japan illustrate how cultural factors may influence the *outcomes*, rather than the *features*, of a clinical syndrome. In a study of abnormal eating behaviors in behavioral FTD patients from Japan and the United Kingdom, the symptoms of abnormal eating were similar, whereas weight gain was more common and severe in the United Kingdom patients [79]. This observation was attributed to differences in food culture, including comparatively higher carbohydrate consumption and caloric intake in the United Kingdom. On a historical note, the Japanese construct *Gogi aphasia,* now accepted as corresponding to semantic FTD, was a syndrome defined by word agnosia and preserved phonological and syntactic aspects of language [80].

There have also been interesting observations pertaining to the interaction between the cultural aspects of language and the language phenotypes of FTD. One study from southern India, where multilingualism is ubiquitous, demonstrated strikingly disproportionate loss of the second

language in multilingual patients with semantic FTD—suggesting that later-learned languages are more vulnerable to neurodegeneration, and that different languages connect to a common semantic network in the brain [81]. A different line of research, also conducted in India, links multilingualism to concepts of cognitive resilience. Multilingual behavioral FTD patients were found to have older age at illness onset than monolingual subjects, after accounting for literacy and urban exposure, whereas multilingual and monolingual subjects with language phenotypes did not differ in age at illness onset [82]. These data were interpreted as support for the proposal that a robust association between multilingualism and executive functions confers resilience to the cognitive decline associated with neurodegeneration.

Finally, it is not unreasonable to speculate that FTD-ALS is comparatively less common in Asia, on account of the relative infrequency of the *C9orf72* mutation. This may have implications for comparisons of FTD survival across regions, given the rapid progression associated with FTD-ALS. To date, geographic differences have not been shown in the progression of symptoms or in survival with FTD—which has ranged 8–10 years across cohorts [83]. However, most of the data on FTD survival have come from European and North American cohorts.

Clinical Care

Clinical care begins with an accurate and complete diagnosis, wherein dementia status, the specific diagnosis (i.e., recognition of FTD), familial status (if pertinent), severity, and pressing needs are clearly identified. The recognition of FTD syndromes at a late stage appears to be a common problem, with geographic differences that are largely shaped by sociocultural and socioeconomic factors. In developing countries, recognition in the community is low and families tend to report cases late due to low health literacy, not being able to take the time from work, and due to the alternative view (often shared by health providers) that dementia is a stage of life [22]. Recognition is frequently low among healthcare providers, who often lack training and share their community's misconceptions about dementia [84, 85]. In North America, Europe, and Japan, diagnostic delay historically reflected lack of familiarity with FTD and its differential diagnosis but, in these regions, the problem is increasingly mitigated by the utilization of tertiary referrals, professional education, peer-led advocacy, and public education through popular media.

Once a diagnosis has been established, the next step is a plan of care that integrates patient and carer education with pharmacologic prescriptions; behavioral, psychotherapeutic, and rehabilitative interventions; and care management [86]. In the later stages, care requires round-the-clock supervision and hands-on assistance, which usually are delivered by relatives or professional aides (or both), or in custodial care. In many low-income countries, such as in much of Africa, pharmacologic prescriptions are often inaccessible due to cost and supply chain barriers. Residential programs are also uncommon, and there is instead a high reliance on informal care from relatives, which is entrenched in cultural norms. In middle-income countries, such as China and India, behavioral and psychotherapeutic programs are available and often integrated into plans of care [87], whereas residential care remains comparatively uncommon. End-of-life care tends to be less formalized in developing countries, and postmortem diagnosis, whether for clinical or research indications, is uncommon.

Conclusions

FTD has been recognized in many regions of the world. The incidence and prevalence vary widely, but this, at least partly, reflects differences in the methods used to undertake the studies, and disparities in the expertise and resources for research. Some of the epidemiological data point to differences in the distribution of genetic risk factors; mutations in *C9orf72*, *GRN*, and *MAPT* are more frequently reported in patients of European descent, whereas they are less common

in those of Asian descent. There appear to be cultural influences on the expression of symptoms, but more research will be needed to clarify the environmental and social mechanisms involved; the interactions of cultural influences with genetic susceptibility factors is not known. The wide variation in care reflects disparities in economic resources and clinical infrastructure, as well as local practices.

There are pressing needs for advancing research on FTD. Population studies are needed in order to fill gaps in our knowledge about FTD frequency and risk factors in developing regions and among minority groups in developed countries, and to facilitate the psychometric characterization of contemporary diagnostic criteria and their translation to different cultural contexts.

The multicentric research collaborations developed in North America (ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration, https://www.allftd.org) and Europe (Genetic FTD Initiative, https://www.genfi.org) are yielding important insights from mutation carriers regarding the biological events involved in the development and evolution of symptoms—and the non-Mendelian genetic susceptibility factors that shape the expression and progression of symptoms. Efforts are now underway to translate these insights to sporadic FTD. It is hoped that reflections on FTD from an international perspective will spur an extension of these vibrant multicenter collaborations, to centers in the developing regions of the world. Movement in this direction will depend on advocacy from the International Society for Frontotemporal Dementias, as well as the research community, with an eye to forming strategic partnerships for research and capacity building.

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Progressive Supranuclear Palsy and Corticobasal Degeneration

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Introduction

The two most common clinicopathologic subtypes of frontotemporal lobar degeneration (FTLD) are characterized by TDP-43 or tau pathology [1]. Tau is a microtubule-associated protein important for stability and functional properties of microtubules. The gene that encodes tau protein (*MAPT*) is located on chromosome 17, and it undergoes alternative splicing of exons 2, 3, and 10 to generate six isoforms of tau [2]. Alternative splicing of exon 10 generates two major classes of tau protein that contain either three (3R) or four (4R) ≈30-amino acid repeats in the microtubule-binding domain of tau. Neurodegenerative tauopathies can be subclassified based upon the predominant type of tau that accumulates in cellular lesions [3]. Pick's disease, a rare frontotemporal dementia with lobar cortical atrophy and neuronal Pick bodies, is characterized by tau composed predominantly of 3R tau, while neurofibrillary tangles that characterize the pathology in Alzheimer's disease and chronic traumatic encephalopathy are composed of a mixture of 3R and 4R tau with distinct ultrastructural properties [4, 5]. Disorders associated with 4R tau are clinically and pathologically heterogeneous and include aging-related disorders, such as aging-related tau astrogliopathy (ARTAG) [6] and argyrophilic grain disease (AGD) [3, 7]. The most common of the neurodegenerative 4R tauopathies are progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), which is the focus of this chapter.

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Progressive Supranuclear Palsy

PSP was described by Steele, Richardson, and Olszewski in a small autopsy series of patients with postural instability, vertical supranuclear gaze palsy, facial and cervical dystonia, as well as dementia. Despite some clinical variability, they shared distinctive pathologic features, including argyrophilic neurofibrillary tangles in select subcortical and brainstem nuclei. [8]. With the advent of tau biochemistry and molecular biology, the pathologic features of PSP have been expanded to include not only neuronal lesions but also glial lesions [3, 9]. The clinical syndromes

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associated with the characteristic tau pathology of PSP have also expanded from the original descriptions and is described later in the chapter.

Epidemiology of Progressive Supranuclear Palsy

The prevalence of PSP is thought to be approximately 6/100,000 patients [10–13]; however, there is a growing understanding that PSP pathology is associated with multiple clinical phenotypes, suggesting that the above figure may require revision. Increased awareness of this fact led to increased age-adjusted prevalence estimates in Europe (8.8–10.8/100,000 patients) [11, 14]. Of note, age-adjusted prevalence estimates from the same city in Japan (Yonogo) adjusted to the census of the earlier study increased from 5.8/100,000 patients in 1999 to 17/100,000 patients in 2010 [15, 16]. This is, in part, due to identification of more phenotypes, since the previous studies used the National Institute of Neurologic Disease and Stroke and Society for PSP (NINDS-SPSP) criteria that only identified the classical PSP phenotype (also named PSP-Richardson syndrome [PSP-RS]).

Clinical Features of Progressive Supranuclear Palsy

In addition to the typical presentation described by Richardson and colleagues (PSP-RS), other phenotypes associated with PSP pathology have been described, including an extrapyramidal disorder mimicking Parkinson's disease (PSP-P), corticobasal syndrome (PSP-CBS), dementia with predominantly frontal characteristics (PSP-F), dementia with speech and language disturbances (PSP-SL), and others. Consequently, the newest clinical criteria for PSP, supported by the International Parkinson and Movement Disorder Society (MDS-PSP criteria), include a wider clinical spectrum [17]. Typical age of onset of PSP is in the seventh decade of life [17–19], and average survival is 5–6 years; however, certain phenotypes are associated with much longer disease durations [19, 20].

Several criteria for PSP were proposed based upon clinical case series [21–24], but the first widely used criteria that were based on autopsy-confirmed cases was reported by Litvan et al. [18] and supported by the NINDS-SPSP. The NINDS-SPSP criteria outlined several core features of PSP-RS. Mandatory features included a gradually progressive disorder with age of onset 40 years of age or later, presence of vertical supranuclear gaze palsy, and/or postural instability with falls within the first year of disease. Both features had to be present for a diagnosis of "probable PSP," and only vertical supranuclear gaze palsy or slowing of saccades and postural instability with falls within the first year of disease was consistent with a diagnosis of "possible PSP."

Regarding vertical supranuclear gaze palsy, restricted downward gaze has been considered most specific for PSP because restricted upward gaze can be seen to a lesser degree in aging [25], Parkinson's disease [26], and other conditions [27–31] like severely restricted upward gaze and slowing of vertical saccades. At more advanced stages, horizontal supranuclear gaze palsy may develop, as well [32]. Vertical supranuclear gaze palsy may be preceded by subtle ocular motor abnormalities, including loss of vertical optokinetic nystagmus [33], "stair casing," and the "round the house sign" [34], where horizontal saccadic excursions interrupt vertical eye movements. Other ocular motor movement abnormalities include hypometric saccades, breakdown of smooth pursuit, and square wave jerks [35]. Loss of vergence is observed early and may contribute to frequent complaints of diplopia [36]. Other eye findings include blepharospasm and eyelid-opening apraxia [37], although these are not usually early features.

Early loss of postural reflexes and falls are common and often an early complaint in PSP-RS, usually occurring within the first year of illness. Falls tend to be backwards, but it can occur in any direction and may be compounded by freezing of gait. Falls can result in significant morbidity due

to lacerations, fractures, or intracerebral bleeding [32, 38].

While these features define the core clinical features of PSP-RS, a number of other clinical features are often observed. Parkinsonism manifested by symmetric akinesia and rigidity with an axial predominance is common. Neck stiffness with retrocollis has been described in early descriptions of PSP, but it is rare [8]. Facial dystonia produces the so-called PSP stare, with decreased blink rate, furrowed and raised eyebrows, and a look of surprise. Inappropriate laughter and crying episodes are often observed (pseudobulbar affect). Early hypokinetic and spastic dysarthria is a secondary feature, which can progress to anarthria in severe cases [39]. Dysphagia occurs relatively early, and it is frequently implicated as a cause of death due to aspiration pneumonia [40, 41]. Cognitive manifestations associated with PSP overlap with corticobasal syndrome and frontotemporal dementia (FTD). The clinical course of PSP is relentless and nearly always is associated with a frontal-subcortical-type dementia.

PSP-RS phenotype is the clinical syndrome most likely to have PSP pathology at autopsy. Because of this, the NINDS-SPSP criteria proved to be specific for PSP pathology [42, 43], but to have relatively low sensitivity [43–45]. This is because PSP pathology can present with other clinical syndromes, and eye movement abnormalities seen in PSP often occur later in the course of the disease and sometimes not at all [19, 20, 46–57]. In one autopsy series, 76% of pathologically confirmed PSP had a clinical syndrome other than PSP-RS [58].

The most common clinical PSP variant mimics idiopathic Parkinson's disease (PSP-P) and makes up about one-third of pathologically confirmed cases [46, 59–62]. These patients have asymmetric resting tremor and asymmetric appendicular bradykinesia and rigidity, making the distinction between PSP-P and Parkinson's disease challenging [46, 59, 60, 62, 63]. As many as one-third of these patients will respond to levodopa and show greater than 30% reduction in the Unified Parkinson's Disease Rating Scale [46, 64–67]. Some also develop levodopa-induced dyskinesias [46]. Most PSP patients have minimal or no response to levodopa therapy, and if a response occurs, it is typically mild and not sustained [20, 24, 68]. Robust and prolonged response to levodopa therapy is an exclusionary criterion for PSP and makes Parkinson's disease a more likely diagnosis [17]. It can be 3–4 years into the disease course before supranuclear gaze palsy is present to aid in refining the diagnosis in PSP-P [19, 62]. PSP-P patients also have a longer disease duration than PSP-RS, with an average survival of 10–15 years [19, 46, 62].

Other syndromes have been described in autopsy-confirmed PSP. Some present with impulsivity and behavioral changes, including apathy, impulsivity, and social inappropriateness akin to behavioral-variant frontotemporal dementia (PSP-F) [53, 69, 70]. Others present with progressive non-fluent aphasia or apraxia of speech (PSP-SL) [48, 52, 70, 71]. About 10% have a corticobasal syndrome with asymmetrical dystonia, myoclonus, apraxia, and cortical sensory loss (PSP-CBS) [55, 56, 70, 72]. Another rare presentation, but one that is highly predictive of PSP pathology, is pure akinesia with gait freezing (PSP-PAGF) [47, 73, 74]. Early presentations currently considered to be "suggestive" of PSP in MDS-PSP criteria are isolated postural instability (PSP-PI) [19, 75] and isolated oculomotor dysfunction (PSP-OM) [19, 20]. The most uncommon presentations are progressive cerebellar ataxia (PSP-C) [51, 76, 77] and primary lateral sclerosis (PSP-PLS) [50, 57]. It is important to note that while some patients present with discrete syndromes, it is common for considerable overlap, and patients also acquire new signs and symptoms as the disease progresses. Regardless of the initial syndrome, most patients develop vertical supranuclear gaze palsy and postural instability, which are core features of PSP-RS, that make diagnosis obvious, but these may occur only later in the disease course in some of the PSP clinical variants [19].

Recognition of the spectrum of clinical heterogeneity in PSP, led the MDS-PSP criteria to incorporate a broader set of symptoms and signs, as well as levels of certainty that would be associated with PSP pathology [17]. These criteria are

more sensitive, but they are less specific than the NINDS-SPSP criteria [78, 79]. The implementation of "multiple allocation extinction" rules (MAX rules) have been necessary to help disentangle patients who may be classified into more than one clinical MDS-PSP category [79]. Even so, these MAX rules may fail to separate up to 40% of patients with PSP-P and PSP-RS overlap syndromes [80]. These issues highlight the ongoing need for specific biomarkers to improve diagnostic accuracy of PSP during life.

Neuropathology of Progressive Supranuclear Palsy

The external appearance of PSP at postmortem evaluation depends upon the clinical syndrome. PSP-RS may have no significant cortical atrophy or mild atrophy affecting the dorsolateral frontal lobe. PSP-F and PSP-CBS usually have more marked frontal atrophy, especially affecting the superior frontal gyrus, while PSP-SL may have more significant frontal atrophy, especially affecting the peri-Sylvian inferior frontal gyrus. Asymmetry, which is not often assessed with research protocols that evaluate only one side of the brain for histology, can be notable in PSP-SL and PSP-CBS. PSP-PLS has focal atrophy affecting the precentral gyrus; it can be asymmetrical as well. The most striking macroscopic finding in PSP-RS (and PSP-P) is midbrain atrophy (Fig. 1a) with loss of neuromelanin pigment on transverse sections of the brainstem (Fig. 1d). The subthalamic nucleus invariably has atrophy (Fig. 1b), and there is also atrophy of the superior cerebellar peduncle (Fig. 1e) and atrophy of the hilus of the cerebellar dentate nucleus (Fig. 1c). Atrophy of subthalamic nucleus and midbrain is usually less severe in PSP-F and PSP-CBS, and often very severe in PSP-PAGF. In the latter, atrophy is frequently accompanied by similar changes in the globus pallidus and with reddish-brown discoloration due to deposition of iron pigment (pallido-nigro-luysial "pigment-spheroid degeneration" [81]).

Histopathologic findings in PSP are similar in the various subtypes. The clinicopathologic subtypes differ in the relative distribution of the neuronal loss and gliosis, and in the density of tau pathology [82]. There are no distinctive cellular pathologies in PSP clinicopathologic variants. The major histopathologic lesions in PSP are neurofibrillary tangles, which often have a globose shape in vulnerable subcortical nuclei, such as the subthalamic nucleus (Fig. 2a) and substantia nigra (Fig. 2b). The morphology and distribution of tangles in PSP is different from the most common disorder with neurofibrillary tangles, Alzheimer's disease (AD), in that subcortical and brainstem nuclei are preferentially affected. The tangles are positive for phospho-tau (Fig. 2d). Using antibodies specific to tau isoforms, the tangles in PSP preferentially accumulate 4R tau (not shown). Tau immunohistochemistry also shows distinctive glial pathology in PSP, including tufted astrocytes (Figs. 2d and 3e) and oligodendroglial coiled bodies (Fig. 2f). Tufted astrocytes are most frequent in neocortex, neostriatum, and midbrain tectum. Coiled bodies are widespread in affected cerebral white matter and vulnerable subcortical fiber tracts in the basal telencephalon, diencephalon, brain stem, and cerebellum. A common neurodegenerative change in the cerebellar dentate nucleus that is not associated with tau pathology is the presence of irregularly swollen cell processes around apical dendrites and cell bodies of cerebellar dentate nucleus neurons (Fig. 2c), a process referred to as grumose degeneration [83]. Glial pathology is increasingly recognized to play a significant role in pathogenesis of neurodegenerative disease, and in PSP microgliosis and astrogliosis parallels the systems affected by neurodegeneration [84], with little evidence to suggest that it precedes tau pathology.

Corticobasal Degeneration

The term corticobasal degeneration was coined by Gibb, Luthert and Marsden [85] to describe the pathology of a rare disorder associated with cognitive and motor features affecting the neocortex and basal ganglia. The clinically defined corticobasal syndrome (CBS) is char-

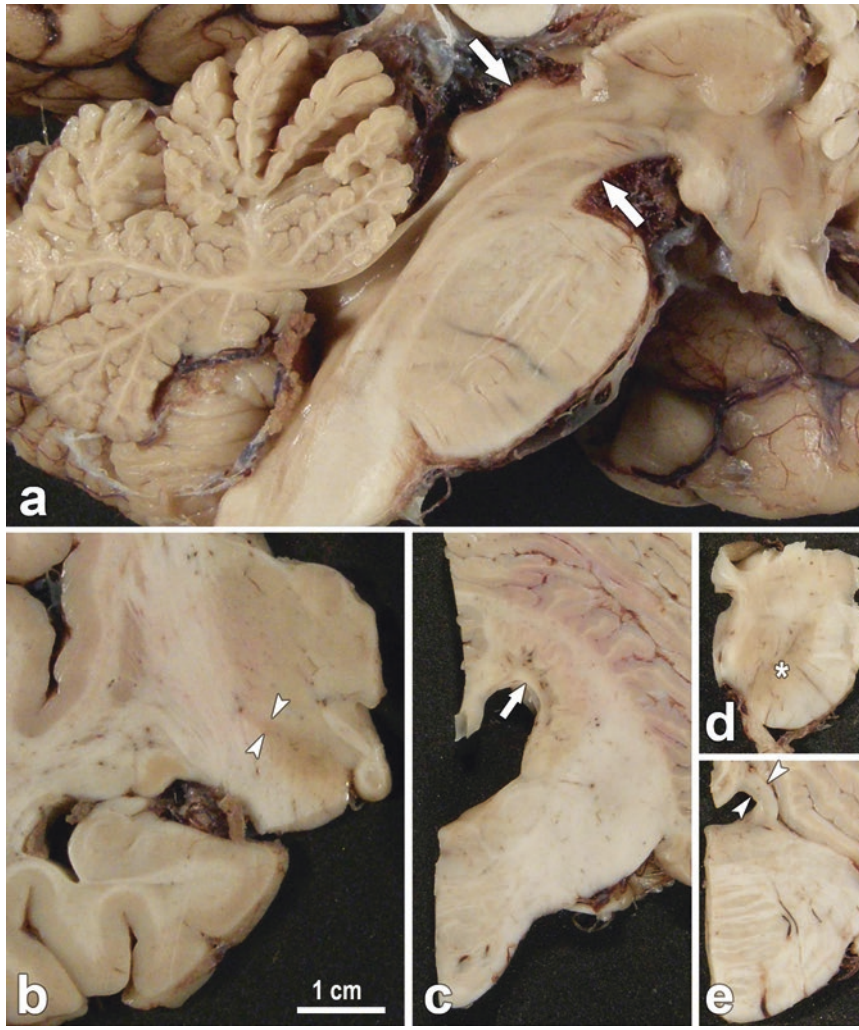

Fig. 1 Macroscopic findings in PSP. (**a**) A sagittal section of the brainstem shows marked atrophy of the midbrain (arrows). (**b**) A coronal section of the diencephalon shows marked atrophy of the subthalamic nucleus (arrowheads). (**c**) A section of the cerebellum at the level of the middle cerebellar peduncle shows marked atrophy and discoloration of the dentate nucleus of the cerebellum (arrow). (**d**) A transverse section of the midbrain shows atrophy and marked neuromelanin pigment loss in the substantia nigra (asterisk). (**e**) A transverse section of the pons shows marked atrophy of the superior cerebellar peduncle (arrowheads)

acterized by progressive cognitive decline associated with asymmetrical rigidity, dystonia, myoclonus, and alien-limb phenomenon. Early autopsy studies reported focal cortical atrophy and swollen achromatic neurons ("ballooned neurons" [86]), as well as neuronal loss in the substantia nigra and cerebellar dentate nucleus—"corticodentatonigral degeneration with neuronal achromasia" [87]. These descriptions did not recognize the tau pathology in CBD because neuronal lesions in CBD are weakly positive or negative with traditional silver impregnation methods. It was not until the early 1990s that widespread tau pathology in CBD was shown to be distinct from Alzheimer's disease, using immunohistochemistry and ultrastructural methods [88–90]. The pathognomonic astrocytic lesion of CBD ("astrocytic plaques") was described in 1995 [91].

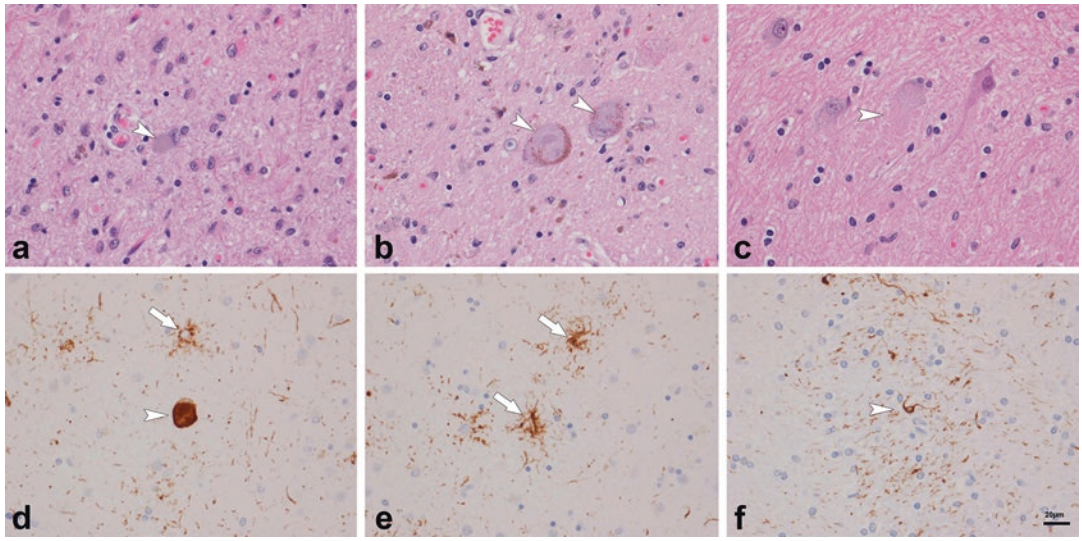

Fig. 2 Microscopic findings in PSP. (**a**) An H&E stained section of the subthalamic nucleus shows severe neuronal loss and astrocytosis, with neurofibrillary tangles (arrow) in residual neurons. (**b**) An H&E stained section of the substantia nigra shows neuronal loss and gliosis with extraneuronal neuromelanin pigment and globose neurofibrillary tangles (arrowheads). (**c**) An H&E stained section of the cerebellar dentate nucleus shows granular eosinophilic swollen cell processes (arrowhead), obscuring the outlines of the neuron, findings characteristic of grumose degeneration (arrow). (**d**) Phospho-tau immunohistochemistry of the caudate nucleus shows a globose neurofibrillary tangle (arrowhead) and a tufted astrocyte (arrow). (**e**) Phospho-tau immunohistochemistry of the caudate nucleus shows several tufted astrocytes (arrows) with morphologic heterogeneity. (**f**) Phospho-tau immunohistochemistry of the internal capsule shows oligodendroglial coiled bodies (arrowhead). All images are of same magnification, bar in (**f**) is 20 μm

Epidemiology of Corticobasal Degeneration

Like PSP, pathologically confirmed CBD has a range of clinical presentations, and CBS may not be the most common. Moreover, the pathologic substrate of CBS is mixed, with PSP being as common as CBD [56, 92], but other disorders, particularly atypical presentations of Alzheimer's disease, can also present with CBS [56, 85, 93–98]. Estimates of prevalence of CBD are inherently flawed. For these reasons, the term corticobasal syndrome (CBS) is now preferred to refer to the clinical presentation described earlier, whereas corticobasal degeneration (CBD) is reserved for the neuropathological diagnosis. The incidence of CBD is estimated to be 0.62–0.92/100,000 [93, 99–101].

Clinical Features of Corticobasal Degeneration Presenting as Corticobasal Syndrome

The onset of CBS is typically in the sixth or seventh decade of life, with a mean survival of about 7 years from diagnosis [93, 99–101]. The motor manifestations of CBS include an asymmetric parkinsonism manifested predominantly by rigidity and bradykinesia [93]. While asymmetry in parkinsonian features is common in Parkinson's disease, the asymmetry in CBS can be striking. There is frequently additional dystonic posturing of the limb. Superimposed may be ideomotor and limb-kinetic apraxia [55, 99, 102]. Alien-limb phenomenon affecting the arm or leg has been described and often results in an unawareness of a levitating hand or leg due to feeling the limb

alien, and more rarely, intermanual conflict [103]. Myoclonus is often present, and it may affect limbs or, rarely, the face [99, 104]. Myoclonus is worsened by action, posture, or stimuli [55, 99, 104]. At times, myoclonus can be difficult to differentiate from tremor, although the quality of myoclonic tremor is jerky rather than the smooth oscillatory tremor observed in Parkinson's disease and other parkinsonian disorders [105]. Postural instability and falls are common, but usually later in the disease course than in PSP, unless the symptoms start in lower extremities [93]. Parkinsonism associated with CBS may benefit from levodopa therapy, but improvement in symptoms is rare and levodopa-induced dyskinesias are also rare [55]. Sustained and robust levodopa responsiveness is an exclusionary criterion to the diagnosis of CBS [93, 106].

Several cognitive features and other signs referable to higher-order cortical function are common in CBS. As previously mentioned, apraxia is a core feature. Ideomotor apraxia is usually one of the first disease features. Some patients develop orobuccal apraxia or apraxia of eyelid opening [99, 104, 107]. Cortical sensory loss with astereognosis and agraphesthesia are frequently observed [108, 109]. Visual neglect may be seen, and it is related to parietal lobe dysfunction [95, 107, 110]. A progressive nonfluent aphasia is also described in CBS, with occasional overlay of apraxia of speech from frontal lobe dysfunction [95, 104, 107, 111]. Other features of frontal lobe dysfunction, such as apathy and disinhibition, are common and early [55, 93].

The clinical presentation of autopsy-confirmed CBD is varied, with some presenting with a cognitive syndrome, and some primarily with a motor phenotype. Other neurodegenerative disorders, PSP and Alzheimer's disease in particular, can present with CBS. Unlike PSP, these initial presentations may not necessarily coalesce into a common phenotype over time, making diagnostics even more challenging. Concomitantly, the clinical diagnosis of CBS has relatively poor predictive value for CBD pathology at autopsy compared to other neurodegenerative disorders. The sensitivity of clinical findings predicting CBD at autopsy is between 26% and56%. The majority of these studies were performed using older criteria; recently, more specific criteria have not been fully vetted [55, 59, 70, 95]. Current clinical criteria for CBD define a gradual progressive disorder with insidious onset and several possible phenotypes, including CBS, a frontal behavioral-spatial syndrome, a variant of primary non-fluent aphasia, and a PSP syndrome. The clinical syndrome of probable CBS is defined as having two of the following signs: limbs with asymmetric rigidity and akinesia, limb dystonia or limb myoclonus, and two of the following signs and symptoms: orobuccal or limb apraxia, cortical sensory deficits, or alien-limb phenomena. Possible clinical CBS involves having one limb with rigidity or akinesia, limb dystonia, or limb myoclonus with one of the above supportive features. A frontal behavioral spatial syndrome is described with the attendant cognitive features. Non-fluent primary progressive aphasia and a PSP phenotype are recognized but considered as possible CBD. Patients with a PSP clinical syndrome must have at least one additional symptom or sign (limb rigidity/akinesia, limb dystonia or myoclonus, apraxia, and cortical sensory loss) [93].

There are multiple exclusion criteria that, if present, make CBD a less likely cause of the clinical presentation. The most important are the presence of genetic mutations in *GRN*, *FUS*, *TARDBP*, *PSEN1/2*, and *APP* genes. Another exclusionary criterion is a cerebrospinal fluid (CSF) Aβ42/tau ratio consistent with Alzheimer's disease [112]. Classic 4–6 Hz parkinsonian resting tremor, hallucinations, dysautonomia, cerebellar signs, the presence of both upper and motor neuron signs, or the semantic or logopenic variants of primary progressive aphasia are also considered exclusionary; they are more likely to indicate Parkinson's disease, dementia with Lewy bodies, multiple systems atrophy, ALS, or FTLD. Lastly, because there are occasional reports of fulminant presentations of CBD [113, 114], imaging consistent with Creutzfeldt-Jakob disease is also exclusionary.

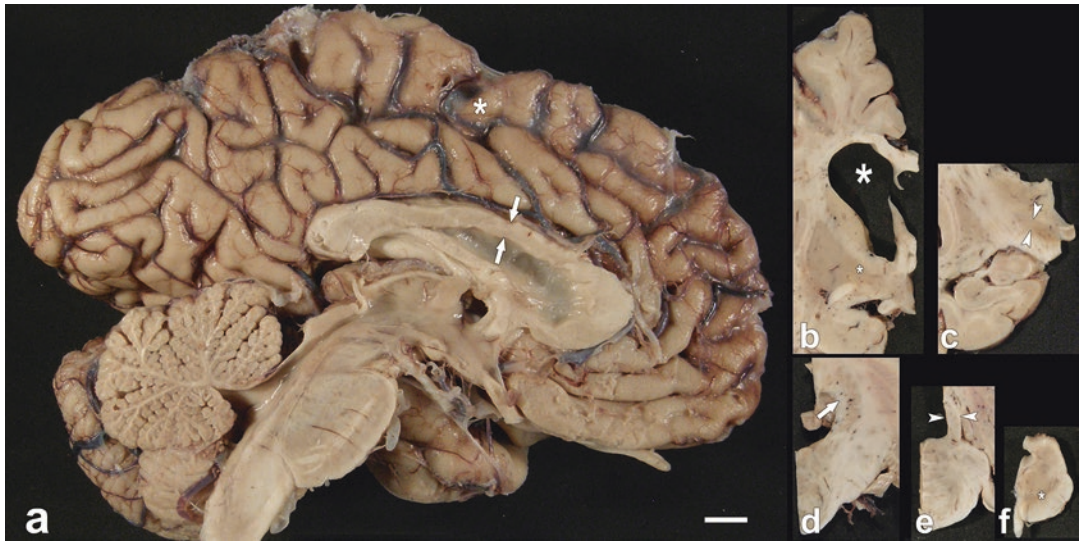

Fig. 3 Macroscopic findings in CBD. (**a**) The medial surface of left hemibrain shows atrophy of the superior frontal gyrus (asterisk indicates area of greatest pathology) and focal atrophy of the corpus callosum (arrows). (**b**) A coronal section of the brain at the level of the fornix shows marked enlargement of the frontal horn of the lateral ventricle (large asterisk). There is also atrophy and discoloration of the globus pallidus (small asterisk). (**c**) A coronal section of the diencephalon and anterior medial temporal lobe shows no hippocampal atrophy and minimal-to-no atrophy of the subthalamic nucleus (arrowheads). (**d**) A section of the cerebellum at the level of the middle cerebellar peduncle shows no atrophy and normal myelin in the hilus of the dentate nucleus (arrow). (**e**) A transverse section of the pons shows no atrophy of the superior cerebellar peduncle (arrowheads). (**f**) A transverse section of the midbrain shows mild atrophy and marked neuromelanin pigment loss in the substantia nigra (asterisk)

Neuropathology of Corticobasal Degeneration

The external appearance of the CBD brain at postmortem evaluation depends upon the clinical syndrome. For patients presenting with CBS or frontotemporal dementia syndromes, there is usually focal atrophy, especially affecting the medial superior frontal gyrus (Fig. 3a). Language-predominant syndromes often have inferior frontal gyrus (peri-Sylvian) atrophy. There is often atrophy of the corpus callosum (Fig. 3a), which tends to parallel the distribution and severity of the focal cortical pathology. Atrophy can be asymmetrical, but this is often difficult to assess at autopsy, given that half the brain is usually frozen for research purposes. Some cases, particularly patients with long tract signs, may have atrophy that extends to the motor cortex. Coronal sections frequently show enlargement of the frontal horn of the lateral ventricle (Fig. 3b). The most common finding in the basal ganglia is atrophy and reddish-brown discoloration of the globus pallidus (Fig. 2b). Unlike PSP, there is usually no significant atrophy of the subthalamic nucleus (Fig. 3c). Similarly, the hilus of the cerebellar dentate nucleus (Fig. 3d) and the superior cerebellar peduncle (Fig. 3e) do not have atrophy. Similar to PSP, there is usually loss of neuromelanin pigment in the substantia nigra (Fig. 3f).

Microscopic examination of atrophic cortical sections shows neuronal loss with superficial spongiosis, gliosis, and usually achromatic or ballooned neurons, which are readily detected with routine histology stains, such as hematoxylin-and-eosin (Fig. 4a). Ballooned neurons are found in middle and lower cortical layers of affected neocortices and have diffuse phospho-tau immunoreactivity (Fig. 4d), as well as intense immunoreactivity with antibodies to alpha-B-crystallin, a small heat-shock protein (not shown), and for neurofilament.

In addition to ballooned neurons, the neocortex and neostriatum in CBD have widespread

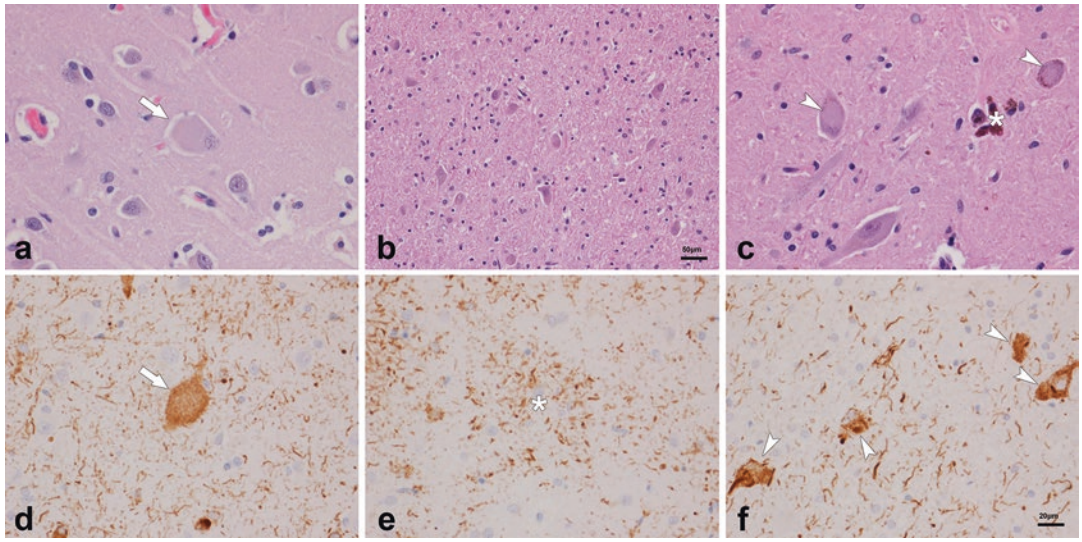

Fig. 4 Microscopic findings in CBD. (**a**) An H&E stained section of superior frontal gyrus shows ballooned neurons (arrow). (**b**) An H&E stained section of the subthalamic nucleus shows mild neuronal loss, but more marked gliosis. (**c**) An H&E stained section of the substantia nigra shows focal neuronal loss (extraneuronal neuromelanin—asterisk) and several neurons with so-called corticobasal bodies (arrowheads). (**d**) Phospho-tau immunohistochemistry of the superior frontal gyrus shows many neuropil threads and a ballooned neuron with diffuse cytoplasmic tau immunoreactivity (arrow). (**e**) Phospho-tau immunohistochemistry of the caudate nucleus shows an astrocytic plaque (asterisk). (**f**) Phospho-tau immunohistochemistry of the subthalamic nucleus shows morphologic heterogeneity of neuronal inclusions (arrowheads). Panels **a** and **c**–**f** are of same magnification, bar in (**f**) is 20 μm. Panel (**b**) is a lower magnification, bar is 50 μm

deposition of tau in both neurons and glia [3, 9]. Glial inclusions are found in both oligodendroglia and astrocytes. The astrocytic lesions have a characteristic plaque-like morphology ("astrocytic plaques" [91]) (Fig. 4e) that is morphologically distinct from tufted astrocytes of PSP. The pathologic feature that best discriminates PSP from CBD is pervasive thread-like cell processes in affected gray and white matter in CBD, to the extent that the difference can be seen by examining the slide with the naked eye (Fig. 5).

The subthalamic nucleus often has at least mild neuronal loss and gliosis (Fig. 4b), but it is rarely as severe as in PSP. Similarly, the substantia nigra has neuronal loss in CBD, but it can be mild (Fig. 4c). Neurons in the substantia nigra may have so-called corticobasal bodies [85] (Fig. 4c). Cortical neurons in atrophic areas have pleomorphic tau-immunoreactive lesions. In some neurons, tau is densely packed into small irregular inclusion bodies. In other neurons, the inclusions are more diffuse ("pre-tangles"). Neurofibrillary lesions in subcortical nuclei, such as the subthalamic nucleus, also typically have marked morphologic heterogeneity (Fig. 4f), while those in the locus ceruleus and substantia nigra can resemble globose neurofibrillary tangles (Fig. 4c).

Pathogenesis of Progressive Supranuclear Palsy and Corticobasal Degeneration

There is no single cause of PSP or CBD, but several environmental and genetic factors have been investigated. The Environmental Genetic PSP (ENGENE-PSP) study found that lower educational attainment, exposure to well water and industrial wastes, and firearm use were related to higher risk of developing PSP [115, 116]. These findings are also supported by a cluster of PSPs that emerged in northern France in an area of

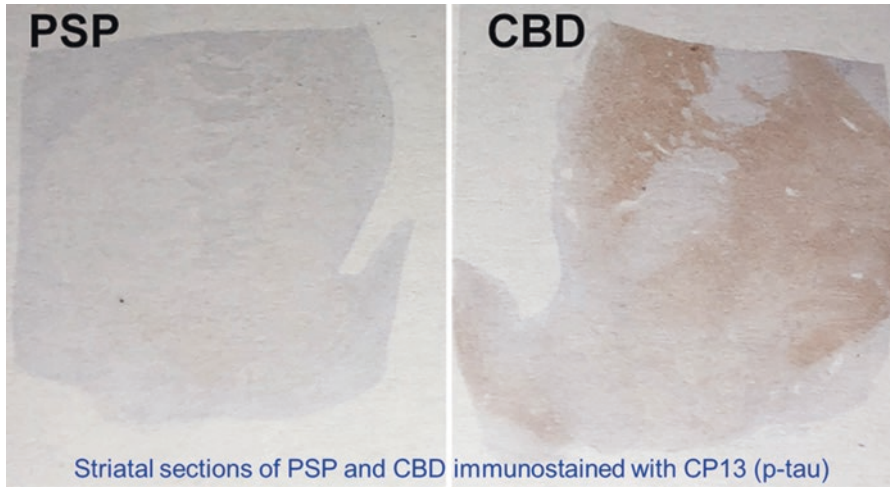

Fig. 5 Comparison of tau burden in PSP and CBD. Sections of the neostriatum in PSP and CBD, immunostained under the same conditions with a sensitive phospho-tau antibody (CP13 from Peter Davies, Feinstein Institute, Long Island, NY), show a clear distinction between PSP and CBD, due to dense tau pathology, mostly thread-like processes (not visible at this magnification), in CBD

high industrial waste contamination [117]. Consumption of high levels of annonacin, a mitochondrial complex I inhibitor, found in the paw-paw fruit was associated with developing PSP or other atypical parkinsonian syndromes in studies in the Caribbean island of Guadeloupe [118, 119]. There may be a slight male predominance within PSP patients [22, 46], and one study documented that increased estrogen exposure in women may be protective against developing PSP [120]. Environmental exposures have not been evaluated in CBD to date.

MAPT mutations may lead to either PSP or CBD [121–124]. Mutations in this gene can also lead to frontotemporal dementia, FTLD with parkinsonism, or primary progressive aphasia [125]. The H1/H1 genotype elevates the risk for developing PSP and CBD [17, 126, 127]. One genome-wide association study in a large cohort of pathologically validated PSP patients additionally identified genetic risk variants at the *MOBP*, *STX6*, and *EIF2AK3* loci [128]. *MOBP*, which encodes for myelin oligodendrocyte-binding protein, is also implicated in CBD and highlights potential importance of white matter [121, 129]. *STX6* encodes for a SNARE protein implicated in fusing vesicles in the Golgi network [130]. *EIF2AK3* encodes for a protein responsible for inhibiting protein synthesis in the face of excess endoplasmic reticulum stress [131, 132]. These genes have been validated in a second genome-wide association study, which additionally identified *SLCO1A2* and *DUSP10* as other genomic loci of interest [133].

Oxidative stress and inflammation can also be demonstrated in PSP and CBD. Mitochondrial enzymatic activity is decreased in both brain tissue and also in skeletal muscle in PSP patients [134–140]. Higher IL-1β and other inflammatory cytokines are found in the brains and CSF of PSP patients and lead to microglial activation [141, 142], which has been implicated in tau deposition [84]. Superoxide dismutase and glutathione, essential antioxidants, are often seen to be elevated in PSP brain tissue, possibly as a defense mechanism [139, 143].

Recent data suggest that misfolded tau oligomers are capable of acting as a template and induce further misfolding of normal monomeric tau leading to larger and larger aggregates, causing cellular damage and ultimately death and likely leading to spreading of disease in a 'prion-like' manner. In vivo animal studies using preformed fibrils [144, 145], human diseased brain homogenates [146], and other techniques [147, 148] have shown distal spread of tau pathology

via trans-synaptic spread [149, 150]. There may be specific "strains" of tau capable of seeding unique tau pathologies [147, 151, 152].

Biomarkers in Progressive Supranuclear Palsy and Corticobasal Degeneration

The clinicopathologic overlap between PSP and CBD and other neurodegenerative diseases makes the discovery of sensitive and specific biomarkers for these diseases of paramount importance.

Magnetic Resonance Imaging PSP is well described to be associated with several features on structural magnetic resonance imaging (MRI). Most recognized is the presence of midbrain atrophy, resulting in the "hummingbird sign" best seen on the mid-sagittal section (Fig. 6) [153], as well as "morning glory sign [154]", or "Mickey Mouse sign [155]". In one study of an autopsy series of pathologically confirmed cases with PSP, multiple systems atrophy (MSA), or Parkinson's disease (PD), 16/22 (72.7%) of PSP cases were able to be correctly identified by a radiologist reviewing conventional MRI that had been performed during life, and the presence of a hummingbird sign or morning glory sign was 100% specific but was 68.4% sensitive [156]. One study, however, that included different clinical variants of PSP found midbrain atrophy to be a feature of the Richardson syndrome variant, but midbrain atrophy was not found to be a biomarker of PSP pathology [157]. The superior cerebellar peduncle is also frequently atrophied in PSP and, consequently, several different ratios comparing brain stem, pons, superior cerebellar peduncle, and middle cerebellar peduncle measurements have been studied to differentiate PSP from other parkinsonian diseases and from healthy controls. A frequent problem with these measurements is that they are often insensitive, and the radiologic signs will only manifest at later stages of the disease after neurodegeneration has progressed to the point of causing these recognizable patterns [158–163]. A more specific technique to assess the superior cerebellar peduncle is with diffusion tensor imaging (DTI). One DTI study did find the superior cerebellar peduncle to be able to accurately distinguish PSP from normal controls [164]. It is unclear whether atrophy of the superior cerebellar peduncle is a feature of PSP pathology or a feature of Richardson syndrome. Another technique that has also been studied in PSP is resting-state functional magnetic resonance imaging (fMRI). Resting-state fMRI studies have demonstrated disrupted thalamocortical connectivity in PSP [165, 166].

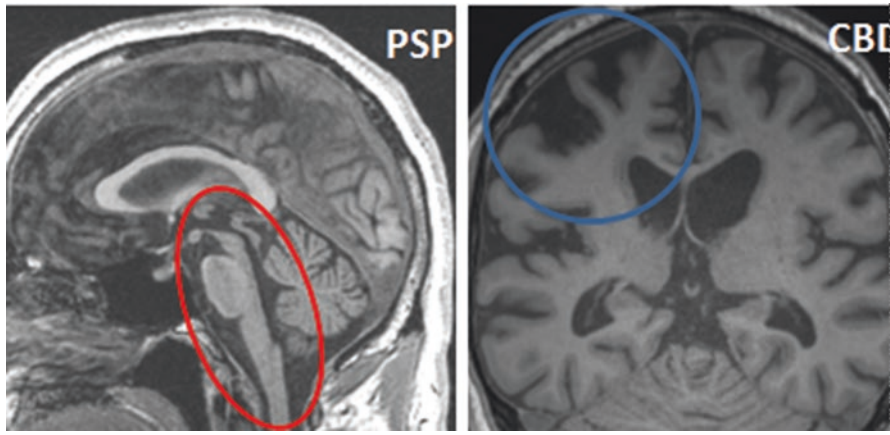

Fig. 6 MRI scan in autopsy-confirmed PSP and CBD. MRI scan in PSP shows the classic hummingbird sign on sagittal MRI, while asymmetric atrophy of the posterior frontal cortex is seen in CBD

Fewer MRI studies have been performed in CBD, but the most frequently cited sign is asymmetric cortical atrophy, affecting the parietal and frontal lobes (Fig. 6) [167–171]. Corpus callosum atrophy is also cited occasionally. Regrettably, neither of these features are specific for CBD to fully differentiate it from other pathologies that cause CBS clinical phenotypes [70, 167, 172]. In addition, symmetric cortical atrophy has been described in autopsy-confirmed cases of CBD [173]. Research studies have utilized voxel-based morphometry to try to distinguish CBD from Alzheimer's disease and other neurodegenerative diseases that present with CBS. These studies have found distinguishing features at the group level [174, 175]. No biomarker exists to distinguish CBD from other neurodegenerative diseases at the single subject level.

Given the prominent white matter degeneration that is common to these conditions, diffusion tensor imaging and white matter volumetric measurements may show more degeneration in PSP and CBD than atypical AD or FTLD TDP-43 that may have overlapping presentations [176–179].

DaTscan A DaTscan is used to detect dopamine transporters on dopamine neurons. DaTscans are typically utilized to differentiate Parkinson's disease from essential tremor. However, DaTscans have been performed in PSP and CBS patients and show a reduction in dopamine transporter receptors. Unfortunately, this finding is nonspecific and can also be seen in other parkinsonian disorders, for example, MSA.

Positron Emission Tomography The most common PET scan is the fluorodeoxyglucose (FDG)-PET scan, which utilizes radioactive glucose to assess for functional integrity of neocortical regions. FDG-PET findings in PSP and CBS tend to mirror findings on MRI. In PSP, hypometabolism is observed in the premotor cortex as well as the midbrain, the latter when present is known as the pimple sign of PSP [180] (Fig. 7). In CBS and CBD, the FDG-PET scan reveals asymmetric frontal and/or parietal hypometabolism (Fig. 7). There are less than a handful of studies on FDG-PET in autopsy-confirmed PSP, CBD, and other 4R tauopathies. One such study found parietal hypometabolism in CBD and premotor hypometabolism in PSP [181]. Several tracers are currently under investigation that bind to the tau proteins, including ^{18}F-5105, ^{18}F-FDDNP, ^{18}F-THK523, ^{11}C-PBB3, and others [182]. ^{18}F-Flortaucipir (formerly AV-1451 and T807) is the most researched tau tracer to date and appears to bind avidly to paired helical filaments in 3R/4R tauopathies, such as AD [183], and exhibits retention patterns in amnestic AD consistent with Braak tau staging [184, 185] and in posterior cortical regions in posterior cortical atrophy patients [186, 187]. However, ^{18}F-Flortaucipir retention appears to be less robust in 4R tauopathies [183, 188, 189]. Increased retention in the basal ganglia and midbrain can be demonstrated in PSP (Fig. 8), but there is off-site binding, which makes individual patient-level distinctions at early stage difficult [184, 190–193]. Similarly, in CBS, mild increases in retention in cortical regions can be demonstrated (Fig. 8) that correlate with postmortem tau findings [194], although this has been reported to occur predominantly in CBS patients who presented with a motor speech disorder [195]. PET tracers targeting activated microglia (^{11}C-(R) PK11195) may aid in assessing inflammation associated with neurodegeneration in PSP and CBD [196, 197].

Biofluid Biomarkers CSF tau species, including measures of total tau (t-tau) and phosphorylated tau (p-tau) tend not to be elevated in PSP [198–200]. One study reported that a ratio of certain tau fragments may aid in distinguishing PSP from healthy controls and other conditions [201], but the findings could not be replicated [202]. CSF neurofilament light chain (NfL) is an intermediate filament, which can be measured from CSF and is a nonspecific measure of neuronal injury [203], but it shows elevation in PSP, CBD, and other parkinsonian syndromes that can aid in differentiating PSP or CBD from Parkinson's disease [200, 204–207]. The sensitivity of the next-generation single-molecule-array assays has

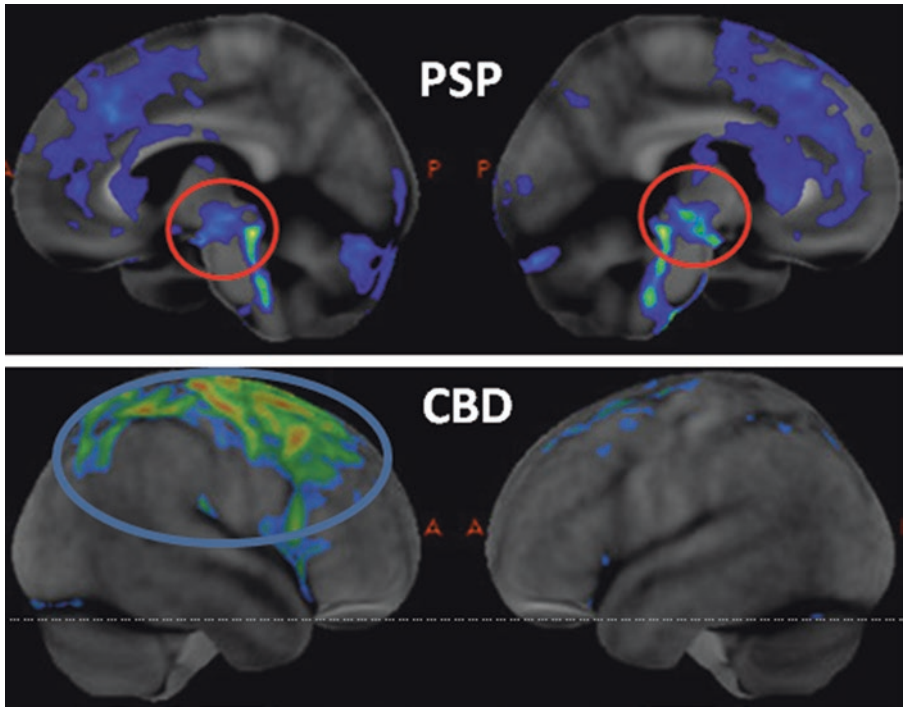

Fig. 7 FDG-PET in autopsy-confirmed PSP and CBD. FDG-PET in PSP shows the classic "pimple sign" (hypometabolism of the midbrain) on mid-sagittal section. Also seen is mild hypometabolism of medial prefrontal and supplementary motor cortex. In CBD, asymmetric frontoparietal hypometabolism is observed on the lateral view

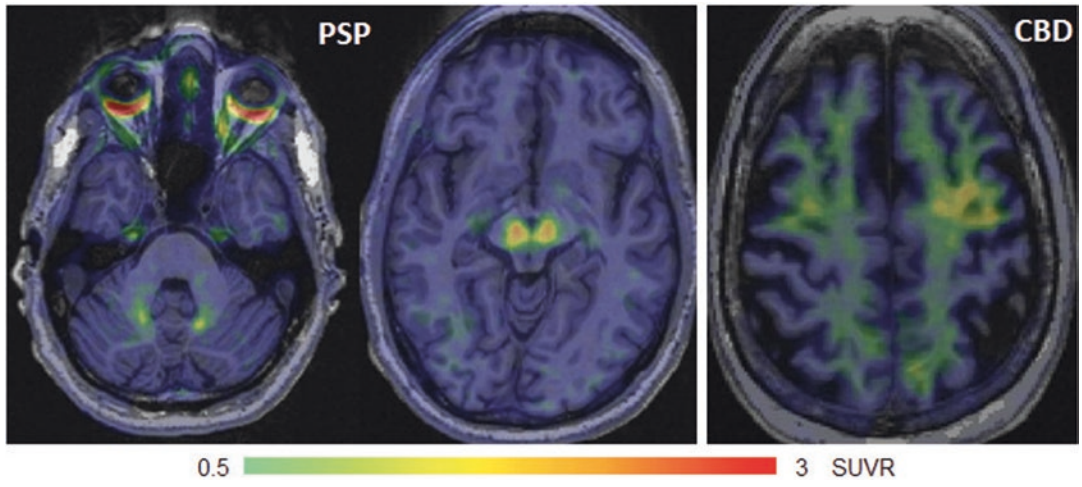

Fig. 8 Flortaucipir PET in autopsy-confirmed PSP and CBD. Flortaucipir PET (AV-1451) in PSP shows increased uptake in the midbrain (substantia nigra) and dentate nucleus of the cerebellum. In a case of CBD that presented with progressive speech apraxia, flortaucipir PET demonstrates asymmetric increased uptake in premotor neocortex

made blood-based NfL measurements possible now as well [208, 209]. Real-time quaking-induced conversion (RT-QuIC) is an emerging assay that was originally developed to aid in diagnosis of Creutzfeldt-Jakob Disease (CJD), where a biologic sample is placed in wells containing monomeric proteins and a fluorescent marker and through polymerization encouraged by sequential shaking steps, can show the presence or absence of a pathologic "seed" from the patient sample. This technique has been adapted to detect alpha-synuclein [210], 3R/4R tau species [211], 3R tau species [212], and a 4R tauopathy assay is under development as well [213], which may offer molecularly specific aid in diagnosis in the near future.

Treatment of Progressive Supranuclear Palsy and Corticobasal Degeneration

Current treatment strategies for both PSP and CBS are supportive and symptomatic as no disease-modulating therapies are currently available for either condition.

Parkinsonism Levodopa preparation may still be trialed to treat the parkinsonism associated with PSP and CBS. In one study of pathologically confirmed PSP patients, approximately one-third of PSP patients showed a significant improvement (> 30% improvement in the Unified Parkinson's Disease Rating Scale) [46], which is a response rate that has been reported in other studies as well [64–67]. Doses of over 1 gm/day of levodopa for 1 month are proposed to elicit responses. Often, however, responses to levodopa are very mild in PSP and CBS, if present at all, and typically wane over time [20, 24, 55, 68, 99, 214]. Dopamine agonists have been trialed in PSP but are generally less effective than levodopa and are more likely to cause side effects [65, 215, 216]. Smaller studies documented improvement in parkinsonism using amantadine or amitriptyline in PSP, but caution is warranted because of possible anticholinergic side effects, including cognitive and psychiatric disturbances, dry mouth, or difficulty with urination [65, 217–219].

Ocular Symptoms Zolpidem showed mild improvements in saccadic speed in one small study of patients with PSP, but those findings have not been replicated [220–222]. Botulinum toxin may be used to treat blepharospasm and eyelid-opening apraxia, but high doses are often required to achieve benefits [223, 224]. Artificial tears and ophthalmic ointments may be used to treat dry eyes, and sunglasses may be of use to aid in photosensitivity symptoms. Alternating an eye patch is useful for double vision, and, occasionally, prism lenses may be fashioned, if the deficits are fixed.

Spasticity, Dystonia, and Myoclonus Muscle relaxants such as baclofen, tizanadine, and cyclobenzaprine may be considered, but they must be carefully weighed against their possible side effects of somnolence [225]. Botulinum toxin may be used for the disabling focal dystonia of the limbs or neck that occurs in both conditions [223, 225, 226]. Clonazepam or levetiracetam can treat the myoclonus associated with CBS as can valproate [214, 227, 228].

Sialorrhea Again, botulinum toxin may be used to treat sialorrhea [229], as can medications including glycopyrrolate or 1% atropine drops placed sublingually, although the latter, if not carefully applied, can be absorbed systemically and cause anticholinergic side effects [230].

Memory Impairments Acetylcholinesterase inhibitors such as donepezil, rivastigmine, or galantamine may offer some mild improvement in memory function, but studies showed that it may worsen gait and dysphagia in PSP and worsen behavioral symptoms in FTD, so it should be used with caution [227, 231, 232]. No studies of memantine in autopsy-confirmed CBD have been performed, but multiple studies of meman-

tine for memory dysfunction in FTD have failed to show benefits [233, 234].

Mood Changes Selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors may be used to treat depression and anxiety, but they are not helpful for the apathy that can accompany PSP or CBS [227]. Dextromethorphan-quinidine is an effective treatment for pseudobulbar affect as are antidepressants [235].

Nonpharmacological Therapies PSP and CBS patients benefit from multidisciplinary care from providers knowledgeable about these conditions. Physical therapy decreases the likelihood of falls and improves global functioning [227, 236–238]. Weighted walkers are often recommended to aid in safer ambulation. Speech therapy may be employed to strengthen vocal muscles but to also provide strategies for more effective communication [239, 240]. Swallowing evaluations are essential if the patient complains of dysphagia or frequent coughing during meals as food consistency or eating habits may be modified. Safety inspections of the home may be helpful and can often be done my occupational therapists who can suggest changes and modifications to promote safety. Social workers are often needed to aid in utilization of resources that may be available to these patients. Lastly, palliative care consultants can help to manage transitions to less aggressive modalities of care and to promote symptom management and navigate end-of-life decision-making in a way that aids in both the patients and the families' quality of life [241].

Experimental Therapies for Progressive Supranuclear Palsy and Corticobasal Degeneration

Although there are no current disease-modulating treatment for PSP or CBD, several medications are under investigation, many of which target the tau protein by different mechanisms: by decreasing production, stabilizing microtubules, promoting immune system clearance, or modifying post-translational changes.

Tau in PSP and CBD commonly undergoes post-translational phosphorylation and acetylation [242]; unfortunately, trials of the GSK-3β kinase inhibitors lithium, valproate, and Tideglusib failed to show efficacy or were stopped due to poor tolerability [243]. Salsalate inhibits tau acetylation in animal models and is currently under early investigation (NCT02422485) [244]. O-Glc-NAC modification and caspase-mediated cleavage are other potential therapeutic targets [245, 246]

The microtubule-stabilizing agent davunetide failed to show efficacy in a phase IIb/III trial [247], and the taxane derivative TPI-287 inducted anaphylactic reactions, which necessitated trial stoppage [248]. Other compounds still under investigation that are thought to work through this mechanism include epothilone-D and methylene blue [249, 250].

Anti-inflammatory medications have been trialed in PSP, including rasagiline, CoQ10, and riluzole, but studies have failed to show efficacy [251–253], although there was significant benefit in a shorter trial using CoQ10 [254].

Tau immunotherapy is actively under investigation. Specifically, in PSP, the BIIB092 antibody product, directed against the N terminus of extracellular tau [255], showed promise in early trials [256, 257], but a phase II study failed to show efficacy (PASSPORT NCT03068468) [258]. Similarly, ABBV-8E12 had favorable early safety results and good target engagement [259, 260] but failed to show efficacy in larger trials. While these results are discouraging, a number of questions remain regarding this strategy, namely if proper epitopes of tau were selected [261, 262], if oligomeric species or intracellular tau should be prioritized although it is technically more challenging [184, 262–267], or if alternative delivery systems may increase blood–brain barrier penetration of antibody products and improve efficacy [184].

Gene therapy through small interfering RNA (siRNA) or antisense oligonucleotides are cur-

rently being investigated in animal models of tauopathies [268–270] and may be of future use in PSP and CBD.

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Tau Protein and Frontotemporal Dementias

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Introduction

Ordered assembly of fewer than ten proteins into filamentous assemblies defines cases of age-related neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD). Aβ, tau, α-synuclein and TDP-43 are the best known of these proteins. For most diseases, the majority of cases are sporadic, but a small percentage is inherited in a dominant manner. Huntington's disease and other polyglutamine repeat diseases form an exception because all cases are inherited. Chronic traumatic encephalopathy (CTE), by contrast, is probably always environmentally induced. Study of dominantly inherited forms of disease has established a causative role for ordered assembly. By extrapolation, it appears likely that inclusion formation is central to neurodegeneration in all cases of disease. Tau proteinopathies, which are characterised by the assembly of tau protein, are the most common proteinopathies of the human nervous system [1].

Frontotemporal dementias (FTDs), also known as frontotemporal lobar degenerations (FTLDs), are characterised by progressive changes in personality and/or language loss, followed by dementia [2]. Their neuroanatomical substrate is degeneration of frontal and temporal lobes of the cerebral cortex. FTDs have a genetic component that is stronger than for most other neurodegenerative diseases, with mutations in *MAPT*, the tau gene, *GRN*, the progranulin gene and *C9orf72*, the chromosome 9 open reading frame 72 gene, being the most common. Mutations in *MAPT* account for approximately 5% of cases of FTD, with an average age of onset of around 50 years and a duration of disease of approximately 10 years. Some of the clinical and neuropathological features resulting from *MAPT* mutations are reminiscent of sporadic tau proteinopathies, including Pick's disease (PiD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), globular glial tauopathy (GGT) and chronic traumatic encephalopathy (CTE). Identification of *MAPT* mutations proved that dysfunction of tau protein is sufficient to cause neurodegeneration and dementia. Here, we first discuss these mutations and their effects, and

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then focus on sporadic PiD, CBD and CTE and their filament structures.

Tau Protein and Its Isoforms

Tau is an intrinsically disordered protein, which may have many interaction partners. It can be divided into an amino-terminal domain, a proline-rich (PXXP) region, the repeat domain and a carboxy-terminal region. The amino-terminal domain projects away from the microtubule surface and is believed to interact with components of the neuronal plasma membrane. It contains a primate-specific sequence between residues 18 and 28. The PXXP motifs in the proline-rich region are recognised by SH3 domain-containing proteins of the Src family of nonreceptor tyrosine kinases, such as Fyn [3].

The repeat region and some adjacent sequences mediate interactions between tau and microtubules. Electron cryo-microscopy (cryo-EM) has shown that each tau repeat binds to the outer microtubule surface and adopts an extended structure along protofilaments, interacting with α- and β-tubulins [4, 5]. Single-molecule tracking revealed a kiss-and-hop mechanism, with a dwell time of tau on individual microtubules of approximately 40 ms [6, 7]. Isoform differences do not influence this interaction. Despite these rapid dynamics, tau promotes microtubule assembly. It remains to be seen if microtubules are also stabilised. Tau is most abundant in the labile domain of microtubules, which has led to the suggestion that it may not stabilise microtubules, but it may enable them to have long labile domains [8, 9]. Less is known about the function of the carboxy-terminal region, which may inhibit assembly into filaments.

Despite lacking a typical low-complexity domain, full-length tau can undergo liquid-liquid phase separation through electrostatic and hydrophobic interactions [10, 11], which has been found in conjunction with amyloid aggregation, at least in vitro. Although liquid-liquid phase separation and amyloid aggregation of tau are independent processes, they may be able to influence each other.

Six tau isoforms ranging from 352 to 441 amino acids are expressed in adult human brain from a single *MAPT* gene [12] (Fig. 1). They differ by the presence or absence of inserts of 29 and 58 amino acids (encoded by exons 2 and 3, with exon 3 being only transcribed with exon 2) in the amino-terminal half, and the inclusion, or not, of the 31 amino acid microtubule-binding repeat, encoded by exon 10, in the carboxy-terminal half. Inclusion of exon 10 results in the production of three isoforms with four repeats (4R) and its exclusion in a further three isoforms with three repeats (3R). The repeats comprise residues 244–368, in the numbering of the 441 amino acid isoform. In adult human brain, similar levels of 3R and 4R tau are expressed [13]; the finding that a correct isoform ratio is essential for preventing neurodegeneration and dementia came as a surprise. The 2 N isoforms are underrepresented in comparison with isoforms that include exon 2 or exclude both exons 2 and 3; 2 N, 1 N and 0 N tau isoforms make up 9%, 54% and 37%, respectively. Big tau, which carries an additional large exon in the amino-terminal half, is only expressed in the peripheral nervous system.

Isoform expression is not conserved between species. Thus, in adult mouse brain, 4R tau isoforms are almost exclusively present, whereas adult chicken brain expresses 3R, 4R and 5R tau isoforms [14]. However, the presence of one hyperphosphorylated 3R tau isoform lacking amino-terminal inserts is characteristic of developing vertebrates. In mice, the switch from 3R to 4R tau occurs between postnatal days 9 and 18, with tau phosphorylation decreasing over time. However, isoform switching and phosphorylation are regulated differently [15]. Adult 4R tau isoforms are better at promoting microtubule assembly and at binding to microtubules than the 3R tau isoform expressed during development.

Tau Assemblies

Full-length tau assembles into filaments [1, 16]. Negative-stain immuno-electron microscopy showed that antibodies specific for the N- and C-termini of tau decorate filaments. This was not

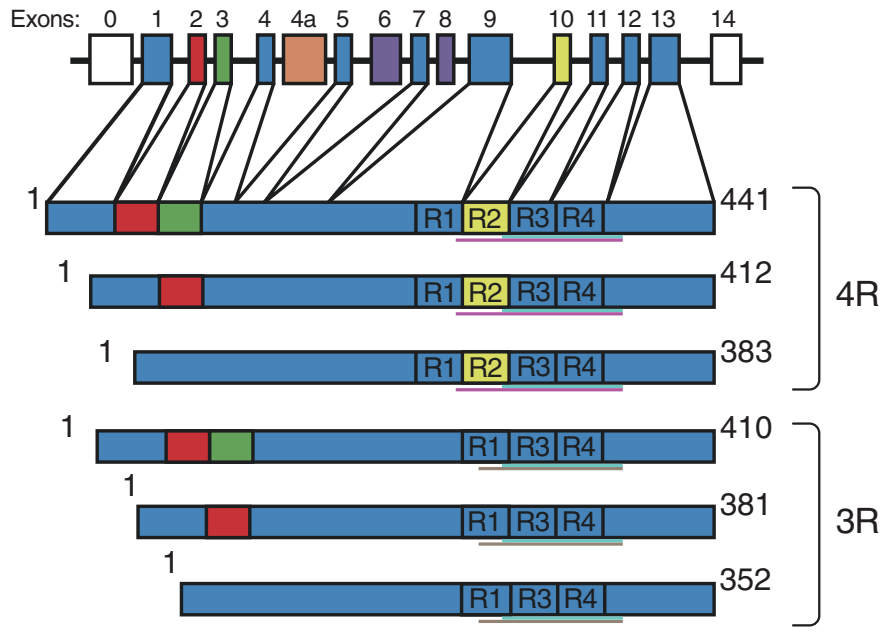

Fig. 1 Human brain tau isoforms. *MAPT* and the six tau isoforms expressed in adult human brain. *MAPT* consists of 14 exons (E). Alternative mRNA splicing of E2 (red), E3 (green) and E10 (yellow) gives rise to six tau isoforms (352–441 amino acids). The constitutively spliced exons (E1, E4, E5, E7, E9, E11, E12 and E13) are shown in blue. E6 and E8 (violet) are not transcribed in human brain. E4a (orange) is only expressed in the peripheral nervous system. The repeats (R1–R4) are shown, with three isoforms having four repeats (4R) and three isoforms with three repeats (3R). The core sequences of tau filaments from chronic traumatic encephalopathy (K274/S305-R379) determined by cryo-EM are underlined (in blue); the core sequences of tau filaments from Pick's disease (K254-F378 of 3R tau) are underlined (in grey); and the core sequences of tau filaments from corticobasal degeneration (K274-E380 of 4R tau) are underlined (in cyan)

the case of antibodies directed against R3 and R4 of tau because their epitopes are occluded in the filaments [17–19]. Together with biochemical studies, this work established that tau filaments consist of a core region and a fuzzy coat. Tau filaments have the biophysical characteristics of amyloid [20]. Because the region in tau that binds to microtubules also forms the filament cores, physiological function and pathological assembly may be mutually exclusive.

Phosphorylation negatively regulates the ability of tau to interact with microtubules, and filamentous tau is abnormally hyperphosphorylated [21]. It remains to be seen if phosphorylation is necessary and/or sufficient for the assembly of tau into filaments. Alternatively, a change in conformation as part of the assembly process may lead to tau hyperphosphorylation. Because tau is hydrophilic, it is not surprising that unmodified full-length protein requires cofactors, such as heparin, to assemble into filaments [22–25]. Cofactors other than heparin and/or post-translational modifications may cause the assembly of tau in human brain [26, 27].

Besides phosphorylation, other modifications may also be involved. Thus, acetylation, methylation, glycation, isomerisation, O-GlcNAcylation, nitration, sumoylation, ubiquitination and truncation of assembled tau have been described. In particular, acetylation of lysine residues has come to the fore in recent years. It reduces charge, which may play a role in filament assembly of tau. Site-specific acetylation of K280 has been shown to enhance tau aggregation, while reducing microtubule assembly [28]. Twenty-one lysine residues are present between residues 244 and 380 of tau.

In AD, CTE, tangle-only dementia and many other tauopathies, all six tau isoforms are present in disease filaments. Pick bodies of PiD are made

of only 3R tau. In CBD, PSP, argyrophilic grain disease (AGD), GGT and several other diseases, 4R tau isoforms make up the filaments. The morphologies of tau filaments vary in the different diseases, even when they are made of the same isoforms.

Genetics of Microtubule-Associated Protein Tau

The relevance of tau dysfunction for neurodegeneration became clear in June 1998, when dominantly inherited mutations in *MAPT* were shown to cause a form of frontotemporal dementia that can be associated with parkinsonism, frontotemporal dementia and parkinsonism linked to chromosome 17 and caused by mutations in the tau gene (FTDP-17 T, also known as familial FTLD-tau) [29–31]. In FTDP-17 T, abundant filamentous tau inclusions are present either in nerve cells or in both nerve cells and glial cells. Aβ deposits, a defining feature of AD, are not present. This work established that a pathological pathway, leading from monomeric to assembled tau, is sufficient to cause neurodegeneration and dementia.

Sixty-five mutations in *MAPT* have been identified in FTDP-17 T (Fig. 2). Filamentous inclusions are composed of either 3R, 4R or 3R + 4R tau [2]. *MAPT* mutations are concentrated in exons 9–12 (encoding R1–R4) and the introns flanking exon 10, with a smaller number of disease-causing mutations in exon 13. Two mutations (R5H and R5L) are present in exon 1 of *MAPT*. Mutations can be divided into those with a primary effect at the protein level and those affecting the alternative messenger ribonucleic acid (mRNA) splicing of tau pre-mRNA.

The architecture of *MAPT* on chromosome 17q21.31 is characterised by two haplotypes as the result of a 900 kb inversion (H1) or noninversion (H2) polymorphism [32]. Inheritance of the H1 haplotype of *MAPT* is a risk factor for PSP, CBD, PD and amyotrophic lateral sclerosis (ALS), but not for PiD [33–38]. The H2 haplotype is associated with increased expression of exon 3 of *MAPT* in grey matter, suggesting that inclusion of exon 3 may protect against PSP, CBD, PD and ALS [39]. In experimental studies, exon 3-containing tau isoforms have been found to aggregate less than those lacking exon 3 [40].

Disease-causing mutations in *MAPT* have made it possible to produce transgenic rodent lines that form tau filaments and show neurodegeneration [41–43]. Aggregation of tau correlates with neurodegeneration [44]. Reducing aggregation and increasing degradation of aggregates are therefore therapeutic objectives. It has been reported that the removal of senescent brain cells leads to a reduction in both tau aggregates and neurodegeneration in transgenic mice [45].

Transgenic mouse lines were also essential for identification of the prion-like properties of assembled tau. Aggregation of hyperphosphorylated tau was induced following intracerebral injection of tau seeds from mice transgenic for human mutant 0N4R P301S tau into transgenic mice expressing wild-type non-aggregated 2N4R tau and, to a lesser extent, following intracerebral injection into wild-type mice [46]. Tauopathy then spread to connected brain regions, indicative of seed endocytosis, seeded aggregation, intracellular transport, and release of tau seeds. This work was complemented by studies in cells [47]. It was subsequently shown that in brain extracts from mice transgenic for human P301S tau, short filaments had the greatest seeding activity [48]. These findings may be mechanistically related to the observation that in the process leading to AD, seed-competent tau inclusions first appear in transentorhinal cortex, followed by the hippocampal formation and large parts of the neocortex [49, 50].

Conformers of assembled tau seem to exist that influence the pattern of spread in brain, reminiscent of prion strains [51–53]. They may explain the variety of human tauopathies. Inclusions formed and spread of pathology occurred after intracerebral injection of brain homogenates from cases of AD, tangle-only dementia, PSP, CBD and AGD into a mouse line transgenic for wild-type human 4R tau and, to a lesser extent, following intracerebral injection into non-transgenic mice [51]. PiD, the filamentous inclusions of which are made of 3R tau only,

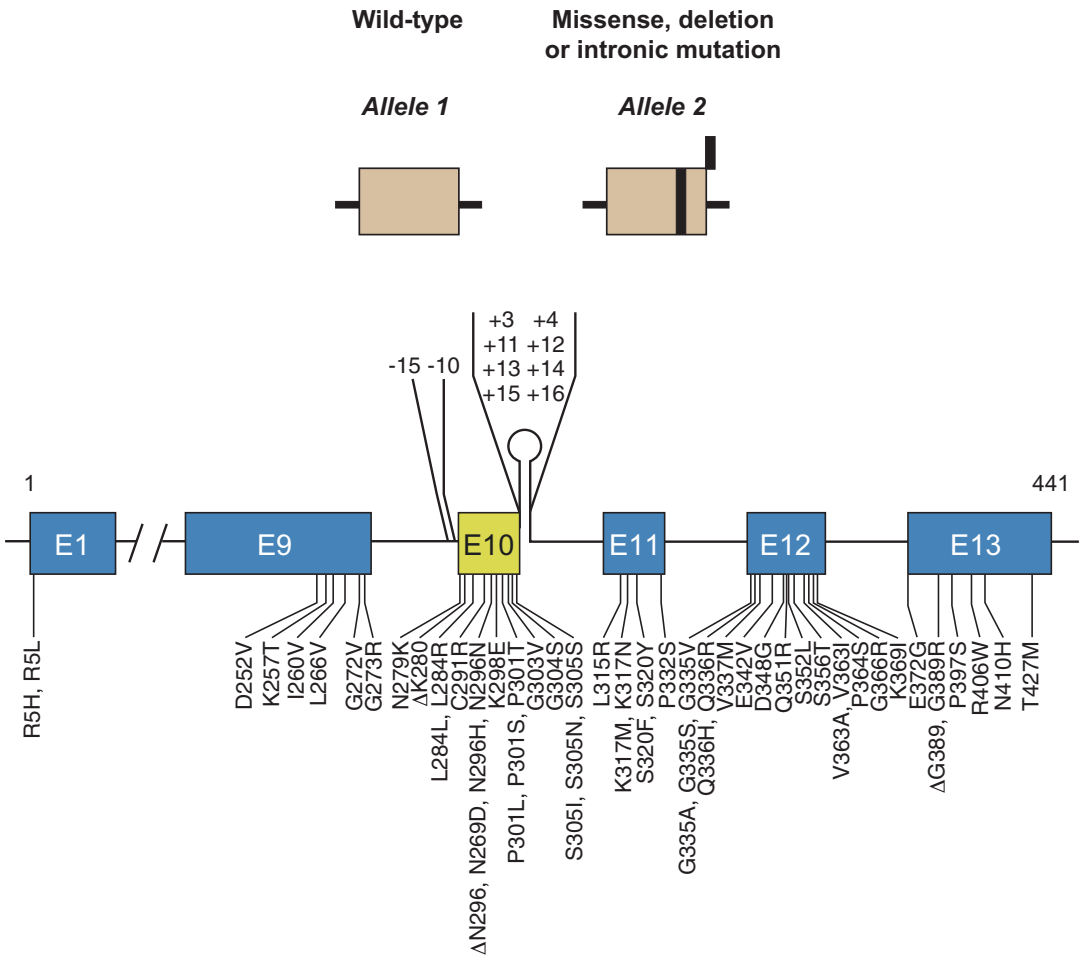

Fig. 2 Mutations in *MAPT* in FTDP-17 T. Missense, deletion and intronic mutations are dominantly inherited. Fifty-five coding region and ten intronic mutations are shown

was an exception. However, seeds from PiD brain induced inclusion formation and spreading in a mouse line, expressing equal amounts of human 3R and 4R tau, in the absence of mouse tau [53].

The tau sequence and, possibly, non-tau molecular requirements for seeded aggregation in vivo remain to be defined. Tau assemblies reminiscent of those in the corresponding human diseases were observed, following the injection of brain homogenates from patients with PSP, CBD and AGD, which are 4R tau proteinopathies [51] and PiD, a 3R tau proteinopathy [53]. Although these findings are consistent with the existence of distinct tau aggregate conformers, structural information is required to prove their existence.

Neuropathological Phenotypes of FTDP-17T

Cases of FTDP-17 T are characterised by the presence of filamentous tau inclusions in nerve cells or in both nerve cells and glial cells [1, 2]. Cases with glial inclusions only have not been described. Tau inclusions are most abundant in hippocampal formation and cerebral cortex.

Inclusions similar to Pick bodies are often observed in the brains of individuals with mutations in exons 9, 11, 12 and 13 of *MAPT*. Similar to sporadic PiD, inclusions associated with mutations G272V in exon 9 and ΔK280 in exon 10 are

made of 3R tau and are not phosphorylated at S262 [54–56]. For other mutations, such as G389R in exon 13, variable amounts of 4R tau and some phosphorylation of S262 are seen in Pick-like bodies [57] (Figs. 3 and 8). Mutation N410H in exon 13 phenocopies the tau pathology of CBD [58].

In the study mentioned earlier, tau deposits are found predominantly in neurons, whereas mutations in exon 1 and exon 10, as well as in the introns following exon 9 and exon 10, are associated with abundant neuronal and glia tau inclusions [2]. Glial pathology is in the form of coiled bodies in oligodendroglia, as well as tufted astrocytes and astrocytic plaques reminiscent of PSP and CBD. Mutations in exon 10 cause the formation of inclusions made of 4R tau; most of these mutations affect exon 10 pre-mRNA splicing, altering the ratio of 3R/4R tau. *MAPT* mutations P301L, P301S and P301T, the primary effects of which are at the protein level, are exceptions (Figs. 4 and 8). They continue to be important for the generation of experimental models of tauopathy and illustrate the clinical and pathological heterogeneity associated with *MAPT* mutations. Although most individuals with mutations P301L and P301S develop behavioural-variant FTD, cases of primary pro-

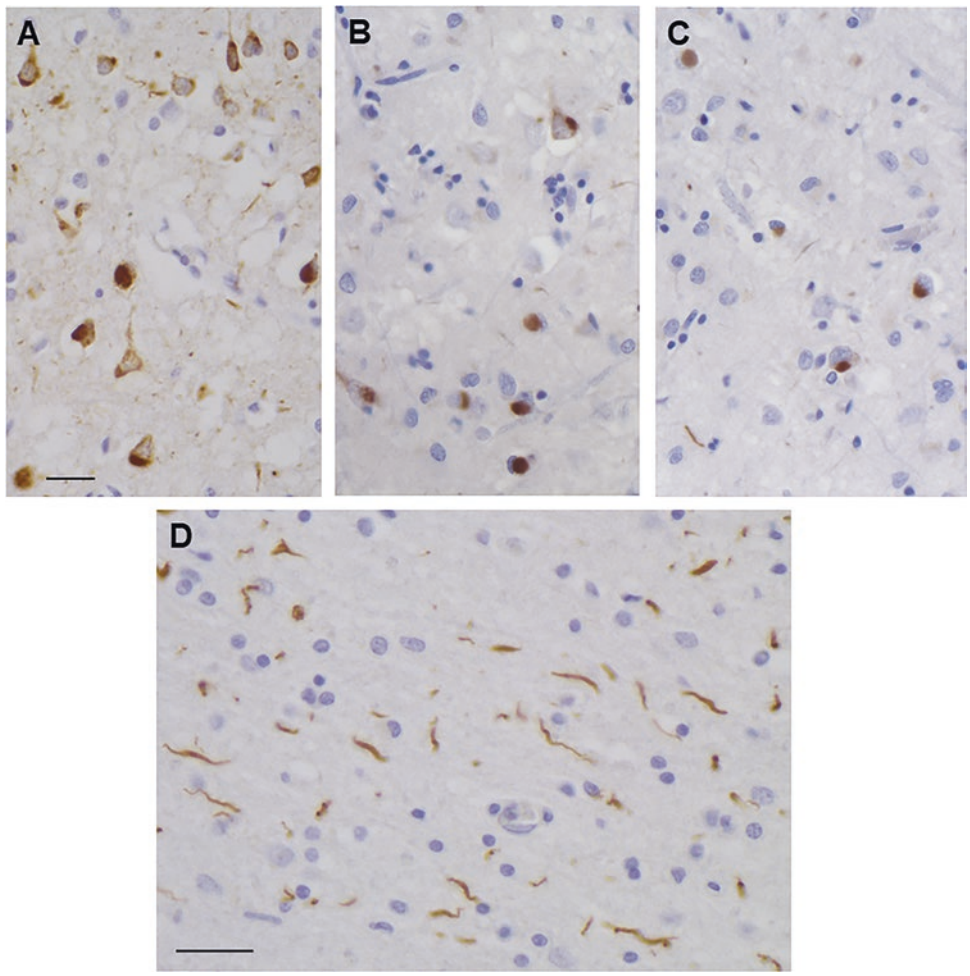

Fig. 3 Tau pathology in the frontal cortex of a patient with the G389R mutation in *MAPT*. Pick-like bodies in grey matter and neuropil threads in white matter are labelled by anti-tau antibodies AT8 (**a**, **d**), RD3 (**b**) and RD4 (**c**). More Pick-like bodies were labelled with RD3 than RD4. Scale bar, 25 μm

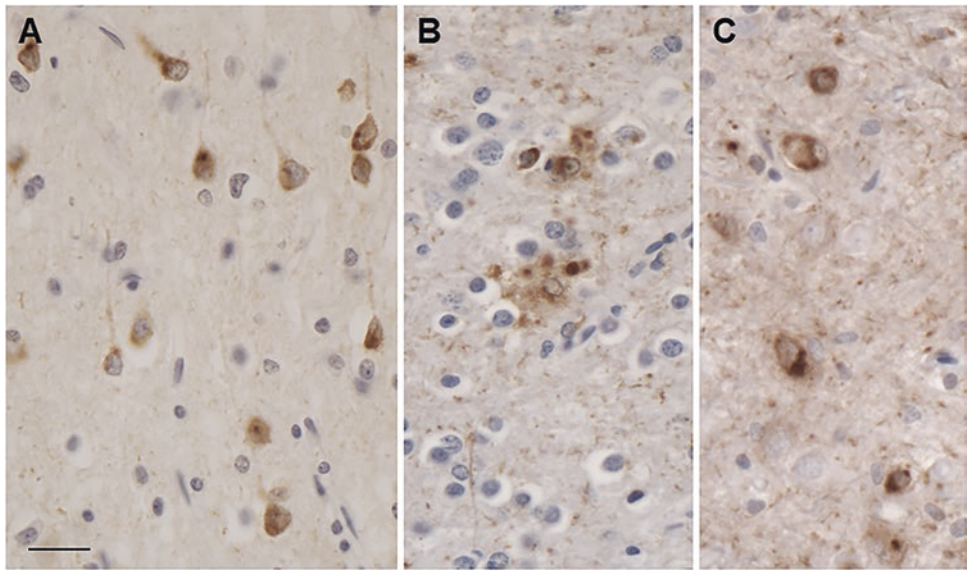

Fig. 4 Tau pathology in the frontal cortex of a patient with the P301L mutation in *MAPT*. Tau inclusions in nerve cells and astrocytes are labelled by anti-tau antibodies AT8 (**a**, **b**) and RD4 (**c**). These inclusions were not labelled by RD3. Scale bar, 25 μm

gressive aphasia have been described [59]. A P301S carrier presented with corticobasal syndrome [60]. A P301L patient had GGT, as had individuals with mutation P301T [59, 61]. GGT has emerged as a common disease associated with mutations in *MAPT*. Mutations in codon 301 affect only 20–25% of tau molecules, with 75–80% being wild type, arguing against a simple loss-of-function mechanism as an important disease determinant [62].

Intronic mutations in *MAPT* and most mutations in exon 10 affect the ratio of 3R/4R tau, which is normally 1:1, without changing the amount of total tau (Figs. 5, 6 and 8). For most mutations, this results in the relative overproduction of wild-type 4R tau and its assembly into filamentous inclusions. Tau filaments appear as twisted ribbons or half ribbons. Although these mutations often give rise to behavioural-variant FTD, cases of atypical PSP have also been described [63]. For other mutations, such as V337M (exon 12) [64] and R406W (exon 13) (Figs. 7 and 8) [65], tau inclusions resemble those of AD, and filaments are made of all six brain tau isoforms.

Structures of Tau Filaments from Pick's Disease

PiD accounts for approximately 20% cases of FTLD-tau. Behavioural-variant frontotemporal dementia and progressive non-fluent aphasia are its most common clinical manifestations. Arnold Pick described the clinical picture and macroscopic findings in 1892 [66], and Alois Alzheimer reported the microscopic features in 1911 [67]. The presence of tau protein in Pick bodies was shown in 1985 [68, 69].

Nerve cell loss predominates in cerebral cortex (frontal > temporal > parietal), followed by hippocampal formation and amygdala, with subcortical structures being affected to variable extents [70]. The substantia nigra may be affected in some cases, while the nucleus basalis of Meynert is mostly unaffected. In frontal and anterior temporal lobes, severe circumscribed (knife-edge) atrophy is commonly seen. Microscopically, the Pick body, which consists of assembled, hyperphosphorylated 3R tau, is the pathognomonic inclusion of PiD (Fig. 9a, b) [71]. Biochemical studies have also suggested the

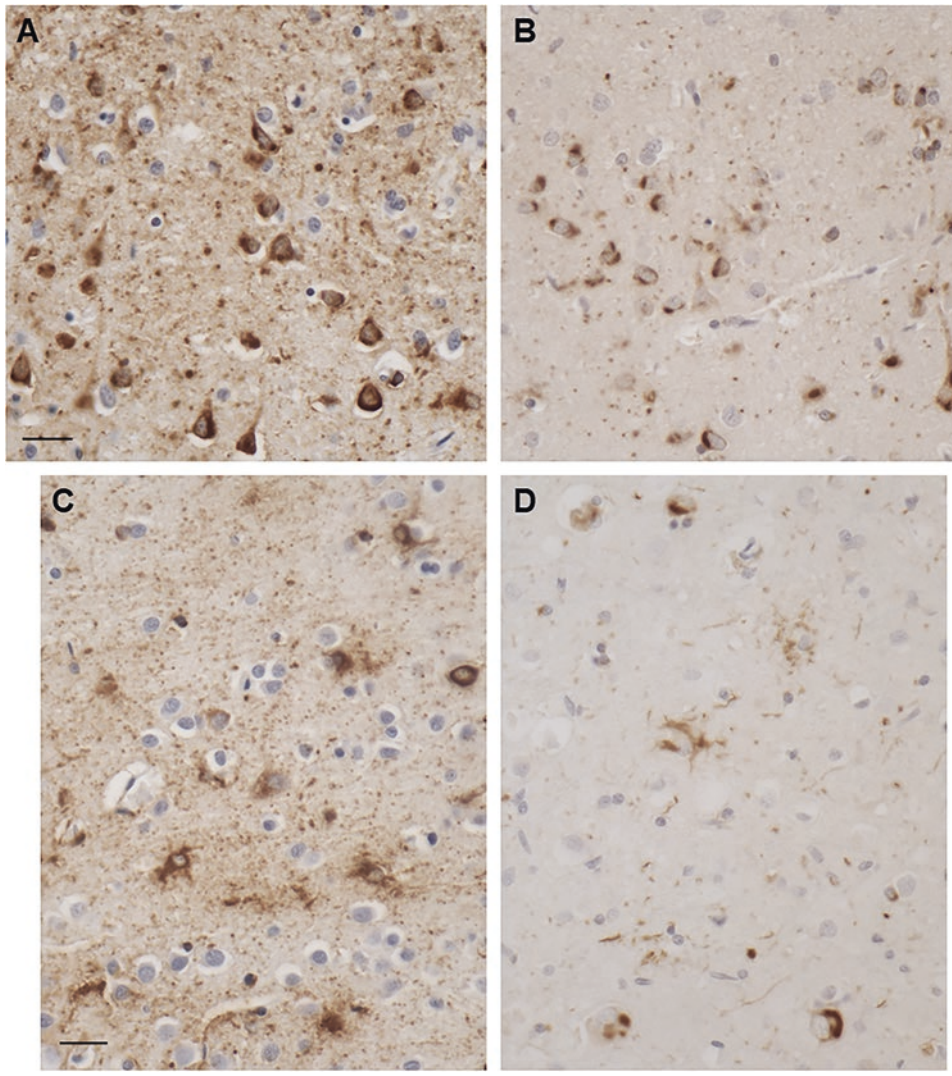

Fig. 5 Tau pathology in the frontal cortex of a patient with the IVS10 + 16 mutation in *MAPT*. Tau inclusions in nerve cells and astrocytes are labelled by anti-tau antibodies AT8 (**a**, **c**) and RD4 (**b**, **d**). These inclusions were not labelled by RD3. Scale bar, 25 μm

presence of 4R tau pathology. However, this probably reflects coexisting pathologies [72] or the presence of a *MAPT* mutation. Pick bodies predominate in hippocampus and cerebral cortex. Fewer assemblies are present in glial cells (Fig. 9c). The glial tau pathology of PiD consists of ramified astrocytes and globular glial inclusions in oligodendrocytes. By Western blotting, assembled tau from PiD brain runs as a doublet of 60 and 64 kDa, which reveals the presence of 3R tau upon dephosphorylation [73].

By negative stain electron microscopy of sarkosyl-insoluble filaments from PiD brain, we observed narrow (Type I) and wide (Type II) tau filaments [74]. Narrow filaments had previously been described as straight, but they have a helical twist with a crossover distance of approximately 1000 Å and widths of 50–150 Å. Wide filaments have a similar crossover distance, but their widths vary from 150 to 300 Å. Immunogold negative-stain electron microscopy showed that most filaments are Type I, with a minority of Type II

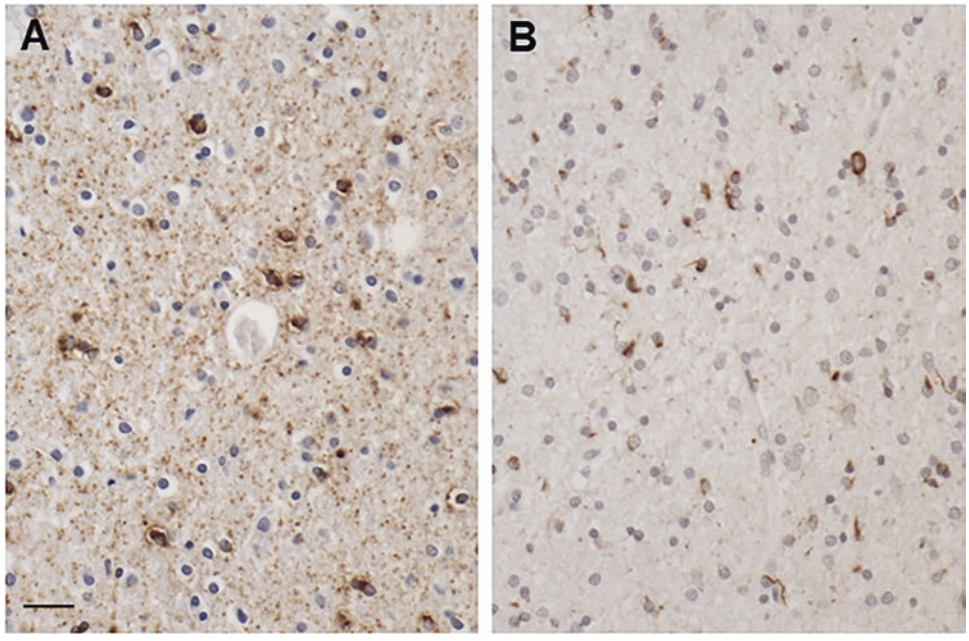

Fig. 6 Tau pathology in the subcortical white matter of the frontal lobe in a patient with the IVS10 + 16 mutation in *MAPT*. Tau inclusions in oligodendrocytes in white matter are labelled by anti-tau antibodies AT8 (**a**) and RD4 (**b**). These inclusions were not labelled by RD3. Scale bar, 25 μm

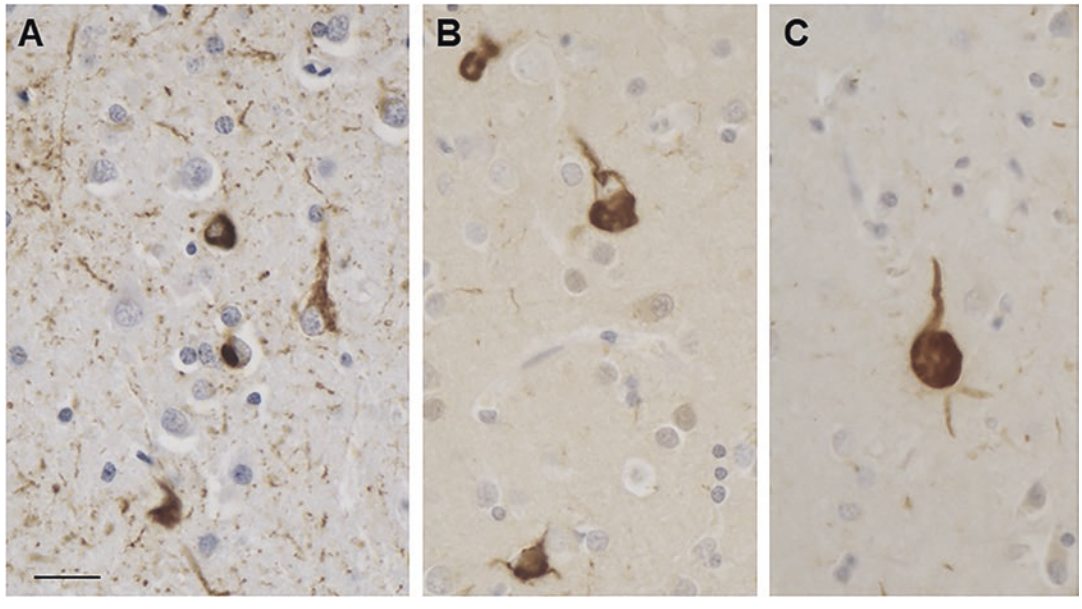

Fig. 7 Tau pathology in the frontal cortex of a patient with the R406W mutation in *MAPT*. Neurofibrillary tangles and neuropil threads are labelled by anti-tau antibodies AT8 (**a**), RD3 (**b**) and RD4 (**c**). Scale bar, 25 μm

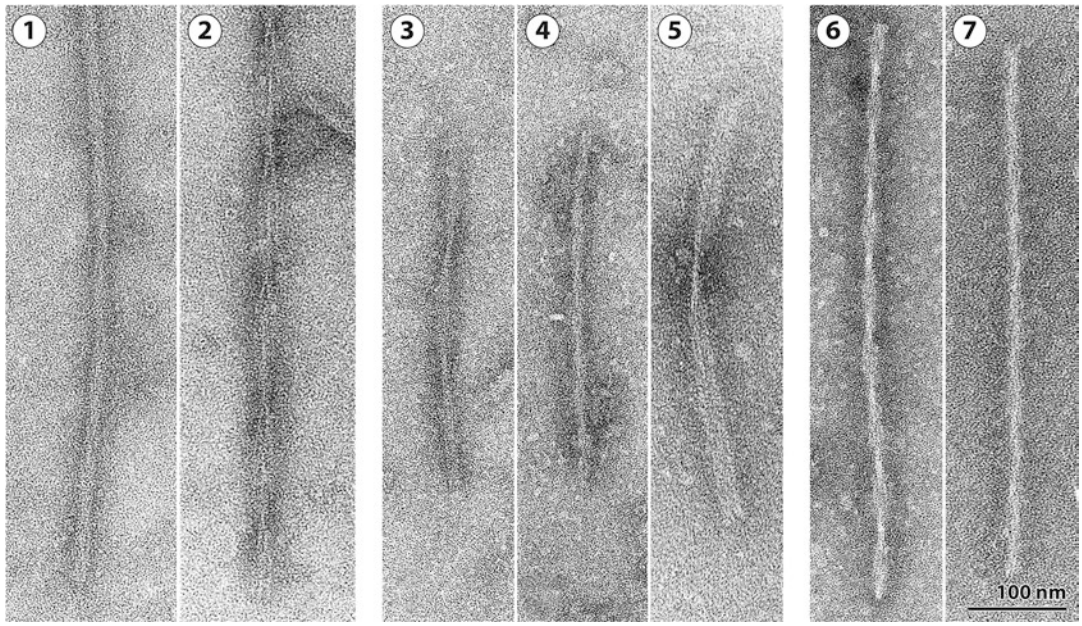

Fig. 8 Negative-stain electron microscopy of tau filaments from cases of frontotemporal dementia and parkinsonism linked to chromosome 17 caused by *MAPT* mutations (FTDP-17 T). (1, 2), Tau filaments from a case with abundant Pick body–like inclusions and a G389R mutation. (1) Straight filaments form the majority species and (2) strongly stranded filaments are in the minority. (3–5), Tau filaments from cases with neuronal and glial inclusions and a P301L mutation or an IVS10 mutation. (3) Narrow twisted ribbons and (4) occasional rope-like filaments. (5) Wide twisted ribbons. (6, 7) Paired helical and straight tau filaments as in AD are present in cases with mutations V337M and R406W in *MAPT*

filaments. Filaments were not decorated by antibodies specific for R1, R3 or R4 of tau, indicating that these repeats form part of the ordered filament core.

By cryo-EM, structures of tau filaments were determined from combined frontal and temporal cortices of an individual with PiD (Fig. 10) [74]. The core of Type I filaments is made of a single protofilament that consists of residues K254-F378 of 3R tau (93 amino acids), which adopt an elongated, J-shaped, cross-β structure (Fig. 10a, c). Type II filaments are formed by the association of two Type I filaments at the distal tips of the J, where they form tight contacts through van der Waals interactions (Fig. 10b). We determined a 3.2 Å resolution map of the ordered cores of Type I filaments; the map of Type II filaments was limited to 8 Å. Each protofilament comprises nine β-strands, which are arranged into four cross-β packing stacks and are connected by turns and arcs. R1 provides two β-strands, and R3 and R4 three β-strands each. The stacks pack together in a hairpin-like fashion: β1 against one side of β8, β2 against β7, β3 against β6 and β4 against β5. The final strand, β9, is formed from the ten amino acids after R4 and packs against the other side of β8.

Three regions of less well-resolved density bordering the solvent-exposed faces of β4, β5 and β9 are apparent in Type I and Type II filaments. They may represent less ordered, heterogeneous and/or transiently occupied structures. The density bordering β4 is similarly located, but more extended, than that found to interact with the side chains of K317, T319 and K321 in tau filaments from AD.

Unlike tau filaments of CBD, CTE and AD, Pick body filaments are not phosphorylated at S262 [75, 76]. The reasons for this differential phosphorylation are unknown. The cryo-EM structure shows that the tight turn at G261 prevents phosphorylation of S262 in the ordered core of PiD filaments, whereas phosphorylated S262 is outside the ordered cores of tau filaments

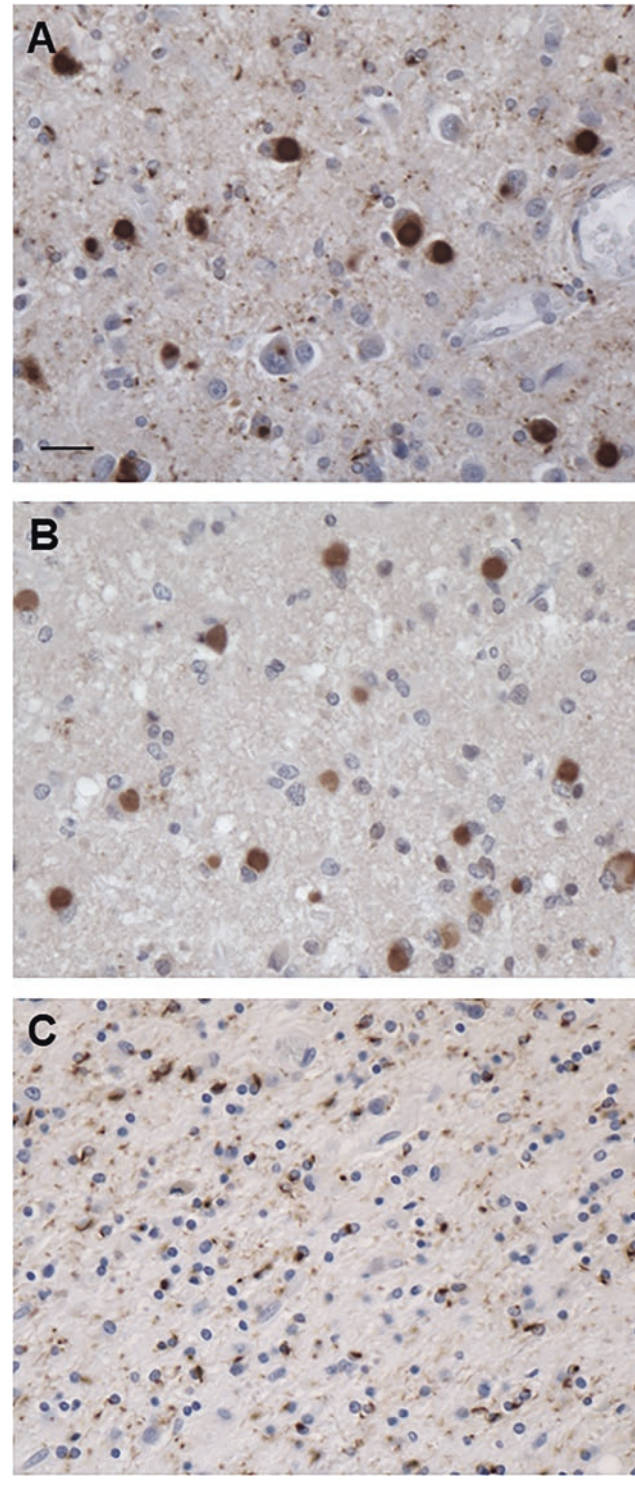

Fig. 9 Tau pathology in the frontal cortex of a patient with Pick's disease. Tau inclusions in nerve cells and glia in grey matter (**a**, **b**), as well as oligodendrocytes in white matter (**c**) labelled by anti-tau antibodies AT8 (**a**, **c**) and RD3 (**b**). These inclusions were not labelled by RD4. Scale bar, 25 μm

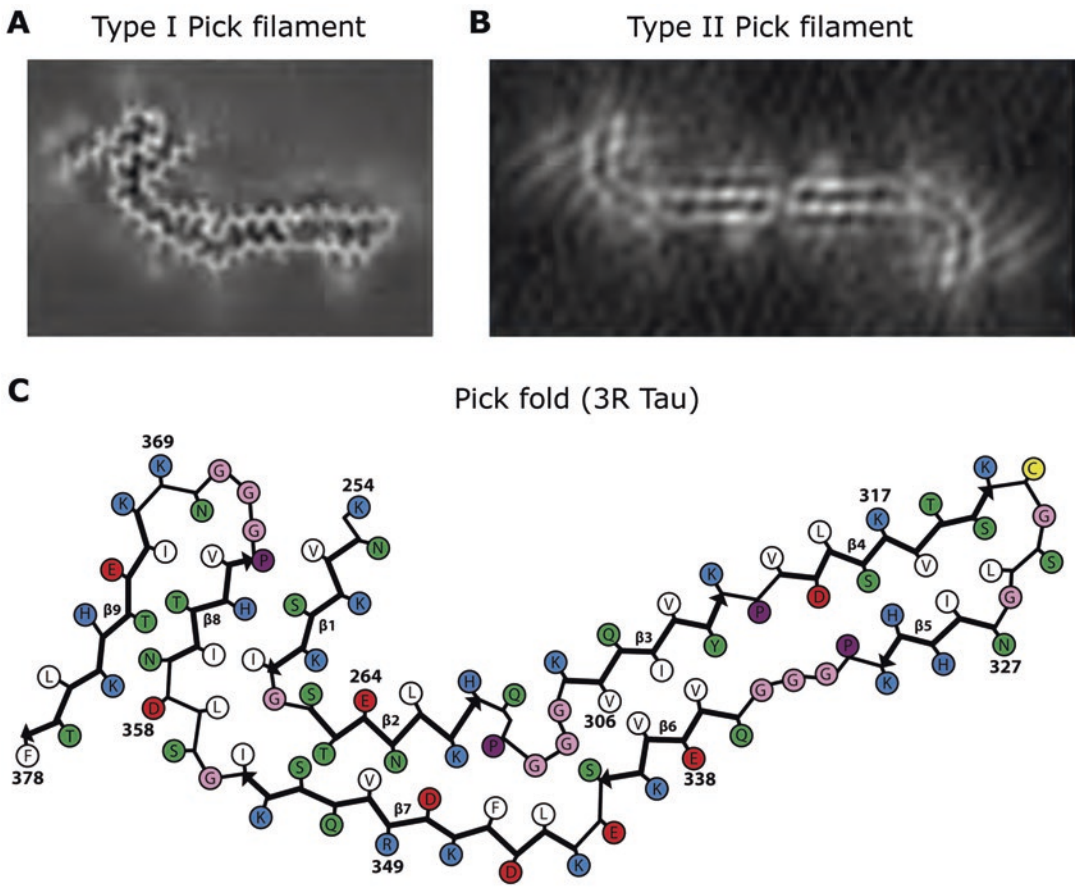

Fig. 10 Structures of tau filaments from Pick's disease. Type I and Type II tau filaments are characteristic, with Type I filaments forming the vast majority (**a**, **b**), Unsharpened cryo-EM densities of Type I (**a**) and Type II (**b**) filaments. Type I Pick filaments contain a single protofilament, whereas in Type II filaments, two identical protofilaments pack against each other symmetrically through Van der Waals interactions at the tip of the J. (**c**), Schematic view of the tau protofilament core of PiD. The observed nine β-strands (β1–β9) are shown as arrows

from CBD, CTE and AD. This may explain the differential phosphorylation and raises the question of whether phosphorylation at S262 may protect against PiD.

It was not previously known why only 3R tau, which lacks R2, is present in Pick body filaments. The above shows that despite sequence homology, the structure formed by K254-K274 of R1 is inaccessible to the corresponding residues from R2 (S285-S305). In support, tau filaments extracted from the brain of the patient with PiD used for cryo-EM seeded the aggregation of recombinant 3R, but not 4R, tau. Such templated misfolding may explain the selective incorporation of 3R tau in Pick body filaments.

Structures of Tau Filaments from Corticobasal Degeneration

CBD typically presents as corticobasal syndrome, which includes cortical signs, asymmetric apraxia, rigidity, myoclonus and alien limb phenomenon. It can also present as behavioural-variant FTD, Richardson's syndrome and posterior cortical atrophy [77]. In 1925, Lhermitte et al. probably described cases of what is now known as CBD [78]. In 1968, Rebeiz et al. reported the disease as 'corticonigral degeneration with neuronal achromasia' [79]. The term CBD was introduced by Gibb et al. in 1989 [80]. The presence of tau protein in the inclusions of CBD was shown in 1990 [81].

Neuropathologically, CBD is characterised by asymmetric focal cortical atrophy and depigmentation of the substantia nigra. Nerve cells show diffuse cytoplasmic tau immunoreactivity, abundant neuropil threads in grey and white matter, as well as pathognomonic astrocytic plaques, mainly in affected cortical areas and in striatum (Fig. 11) [82, 83]. By Western blotting, assembled tau from CBD brains runs as a doublet of 64 kDa and 68 kDa, which consists of 4R tau upon dephosphorylation [84]. In addition, two closely related tau bands of approximately 37 kDa are typical of CBD [85].

By negative stain electron microscopy of sarkosyl-insoluble filaments from CBD brains, we observed narrow (Type I) and wide (Type II) tau filaments [86], in agreement with previous findings [87]. Narrow filaments have a helical twist with a crossover distance of approximately 1000 Å and widths of 80–130 Å. Wide filaments have a crossover distance of approximately 1400 Å and widths of 130–260 Å. Immunogold negative-stain electron microscopy showed that Type I and Type II filaments are present in similar amounts in some cases of CBD, with Type II filaments being more abundant in others. Filaments were not decorated by antibodies specific for R2, R3 or R4 of tau, indicating that these repeats form part of the ordered filament cores.

Structures of tau filaments were determined by cryo-EM from the frontal cortex of three individuals with CBD (Fig. 12) [86]. The core of Type I

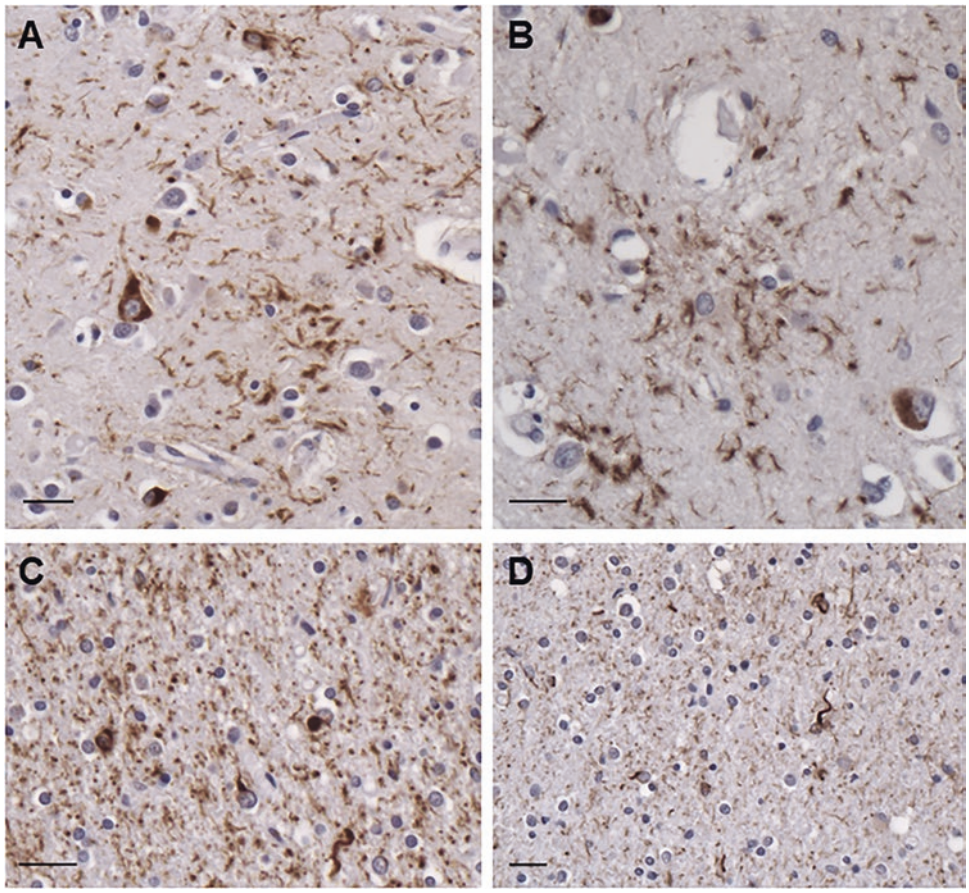

Fig. 11 Tau pathology in the frontal cortex of a patient with corticobasal degeneration. Tau inclusions in nerve cells and glia in grey matter (**a**, **b**), as well as oligodendrocytes in white matter (**c**, **d**) labelled by anti-tau antibodies AT8 (**a**, **c**) and RD4 (**b**, **d**). These inclusions were not labelled by RD3. Scale bars, 25 μm

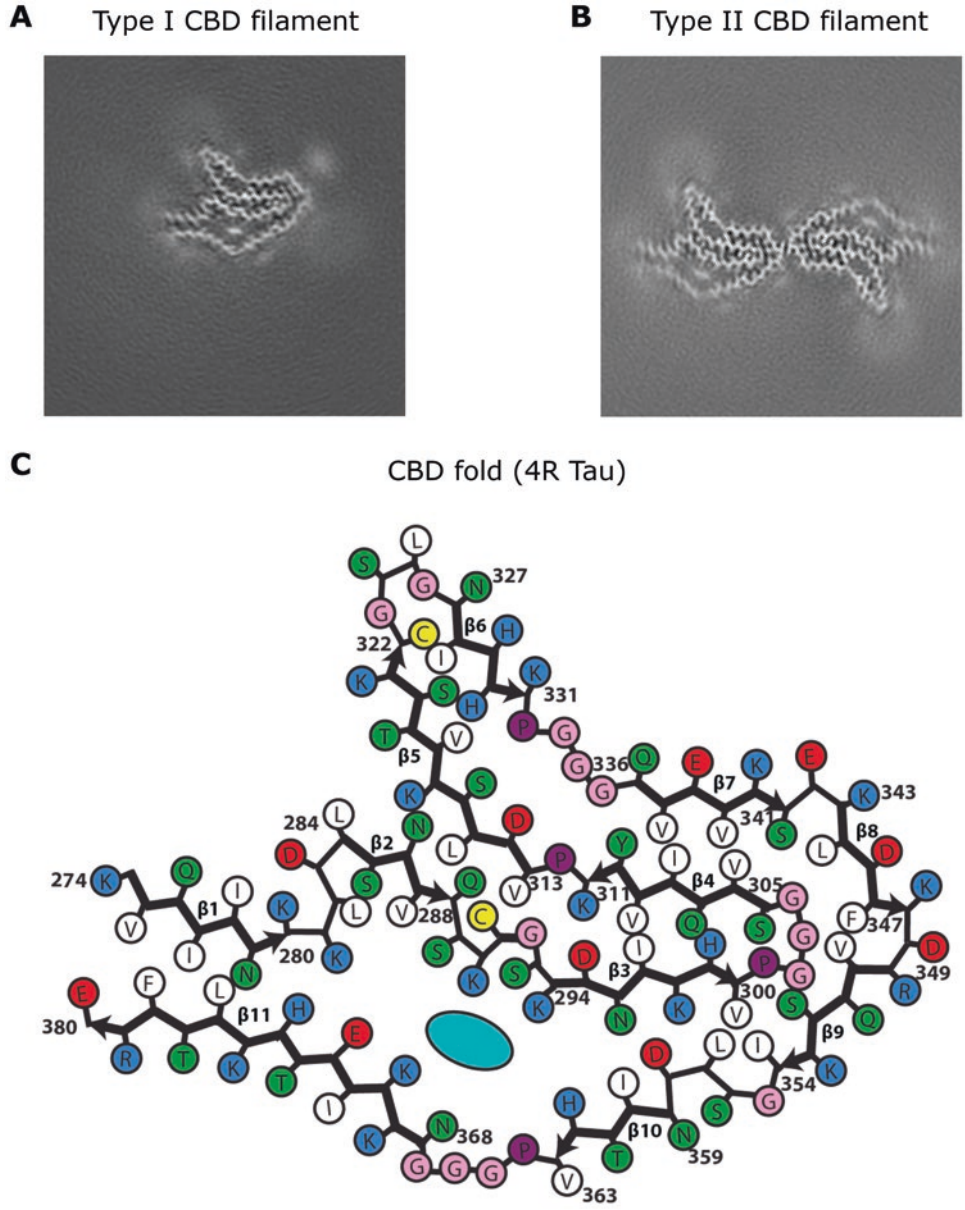

Fig. 12 Structures of tau filaments from corticobasal degeneration. Type I and Type II tau filaments are characteristic, with Type II filaments being more numerous in some cases. (**a**, **b**), Unsharpened cryo-EM densities of Type I (**a**) and Type II (**b**) filaments. Type I filaments contain a single protofilament, whereas two symmetrically packed protofilaments are present in Type II filaments. The protofilament interface is formed by anti-parallel stacking of ^{343}KLDFKDR^{349}. (**c**), Schematic view of the tau protofilament core of CBD. The observed 11 β-strands (β1–β11) are shown as arrows. The central non-proteinaceous density is shown in blue

filaments is made of a single protofilament that consists of residues K274-E380 of 4R tau (107 amino acids; Fig. 12a, c). It encompasses the last residue of R1; all of R2, R3 and R4; as well as 12 amino acids after R4. In the core, there are 11 β-strands (β1–β11): three from R2 (β1–β3), three from R3 (β4–β6), four from R4 (β7–β10) and one from the sequence after R4 (β11). Each protofila-

ment of CBD contains an additional density that is surrounded by the density of tau protein within a positively charged environment. The molecular identities of this density, as well as of those present on the outside of filament structures, remain to be identified. It has been suggested that they may correspond to post-translational modifications of tau [88]. Type II filaments consist of pairs of identical protofilaments of Type I (Fig. 12b). We obtained maps of Type I and Type II filaments at overall resolutions of 3.2 Å and 3.0 Å.

The 11 β-strands of each protofilament are connected by arcs and turns and form a four-layered structure. The central four layers are formed by β7, β4, β3 and β10. Strands β3 and β4 are connected by a sharp turn, whereas β7 and β10 are connected through β8 and β9, which wrap around the turn. On the other side, β2, β5 and β6 form a three-layered structure. β2 packs against one end of β5, and β6 packs against the other end. The first and the last strands, β1 and β11, pack against each other and close a hydrophilic cavity formed by residues from β2, β3, β10, β11 and the connections between β1 and β2, as well as between β2 and β3.

Each tau repeat contains a PGGG (proline-glycine-glycine-glycine) motif. In the CBD fold, that of R1 (residues 270–273) is located just outside the structured core. The PGGG motif of R2 (residues 301–304) forms a tight turn between β3 and β4, which is essential for the formation of the four-layered cross-β packing. The PGGG motif of R3 (residues 332–335) adopts an extended conformation between β6 and β7, compensating for the shorter lengths of these strands compared to the opposing β4 and β5 connected by P312. The PGGG motif of R4 (residues 364–367) adopts a similar extended conformation, forming part of the hydrophilic cavity.

In CBD Type II filaments, protofilaments are related by C2 symmetry. Their interface is formed by anti-parallel stacking of ^{343}KLDFKDR^{349}. Besides van der Waals interactions between the anti-parallel side chains of K347 from each protofilament, the side chain of K347 is positioned to form hydrogen bonds with the carboxyl group of D348 and the backbone carbonyl of K347 on the opposite protofilament.

CBD is characterised by abundant neuronal and glial inclusions of 4R tau. It remains to be determined if Type I and Type II filaments are differentially distributed between neuronal and glial inclusions. This notwithstanding, a single tau protofilament is characteristic of these inclusions.

Structures of Tau Filaments from Chronic Traumatic Encephalopathy

CTE is associated with repetitive head impacts or exposure to blast waves. Described as punch-drunk syndrome by Martland in 1928 [89] and dementia pugilistica by Millspaugh in 1937 [90], CTE has since been identified in former participants of other contact sports, ex-military personnel and after physical abuse. Critchley used the term in a book chapter in 1949 [91]. CTE is the best-known example of an environmentally induced neurodegenerative disease.

Clinically, CTE is characterised by behavioural, mood, cognitive and motor impairments [92]. Initial mood and behavioural changes that progress to marked cognitive impairment are often seen. For this and other reasons, we decided to include CTE in the present discussion, even though it is not generally classified under the umbrella of FTD. Motor impairments, including parkinsonism and cerebellar ataxia, have been described mostly in retired boxers.

The neuropathological concept of CTE was emphasised by Corsellis et al. in 1973, who identified generalised cerebral atrophy and widespread cortical neurofibrillary lesions in some retired boxers [93]. Antigenic similarities between the neurofibrillary lesions of CTE and Alzheimer's disease were noted in 1988 [94]; this was followed by the description of tau inclusions using immunohistochemistry [95]. CTE is defined by an abundance of hyperphosphorylated tau in neurons, astrocytes and cell processes around small blood vessels (Figs. 13 and 14). Together with the accumulation of tau inclusions in cortical layers II and III [96], this distinguishes CTE from Alzheimer's disease and other tauopa-

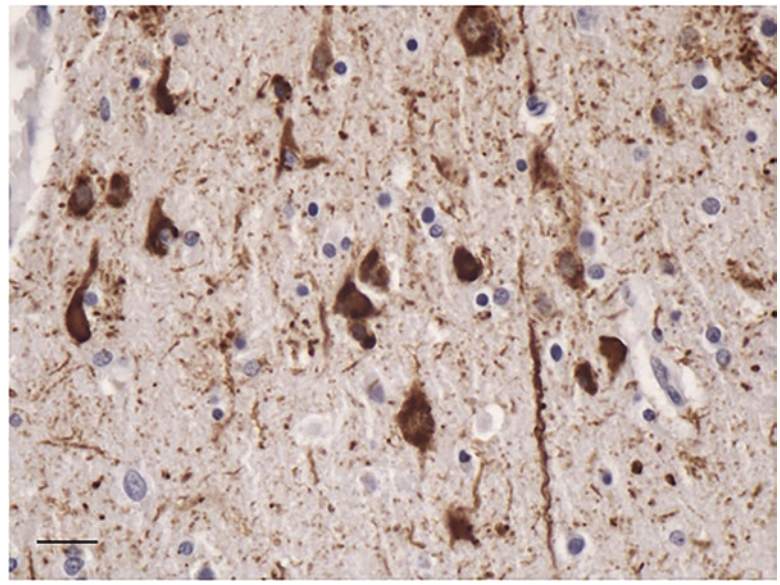

Fig. 13 Tau pathology in the temporal cortex of a patient (former American football player) with chronic traumatic encephalopathy. Tau inclusions in nerve cells and neuropil threads labelled by anti-tau antibody AT8. Scale bar, 25 μm

thies. By Western blotting, assembled tau from CTE runs as major bands of 60 kDa, 64 kDa and 68 kDa, which consist of all six brain tau isoforms upon dephosphorylation [97].

By negative-stain electron microscopy of sarkosyl-insoluble material from CTE brains, it was shown that Type I tau filaments make up about 90% of filaments [98]. They differ from tau filaments of PiD, CBD and AD [74, 86, 99]. Widths are 20–25 nm and crossover spacings 65–80 nm. The remaining filaments (Type II) resemble paired helical filaments of Alzheimer's disease; they have pronounced helical twists that result in projected widths of 15–30 nm.

Structures of tau filaments were determined by cryo-EM from the frontal cortex of three individuals with CTE (one former American football player and two ex-boxers) (Fig. 15). The core of Type I filaments is made of pairs of identical protofilaments that consist of residues K274/S305-R379 of tau (74 amino acids) (Fig. 15a). The protofilament structure (CTE fold) is similar to the C-shaped Alzheimer fold [99], but it adopts a more open conformation (Fig. 15c). Most notably, additional density—which is not present in the Alzheimer fold—is surrounded by the density of tau protein within the ordered core. Analysis of the minority Type II filaments revealed the presence of two kinds of filament, something that was not apparent by negative staining. Approximately 75% of these filaments (Type II) were composed of pairs of the same protofilament as in Type I tau filaments (including the extra density) but with a different protofilament interface. CTE Type I and Type II filaments are thus ultrastructural polymorphs that have different protofilament interfaces, but a common protofilament structure. The remaining filaments were identical to paired helical filaments of Alzheimer's disease. This shows that cryo-EM was able to resolve what looked like paired helical filaments by negative staining into CTE Type II filaments and paired helical filaments. By cryo-EM, paired helical filaments made up 1–2% of filaments.

Each CTE protofilament is C-shaped and contains eight β-strands, five of which give rise to two regions of anti-parallel β-sheets, with the other three forming a β-helix. The carboxy-terminal residues of R1 and R2 form part of the first β-strand. R3 contributes three and R4 four β-strands, with the final β-strand being formed by the 11 amino acids after the end of R4; β1 and β2 pack against β8, β3 packs against β7, with β4, β5 and β6 giving rise to the C-shaped β-helix. The CTE fold is similar to the Alzheimer fold [98, 99], with the main differences being present at the tip of the C, where the packing of β4–β6 coin-

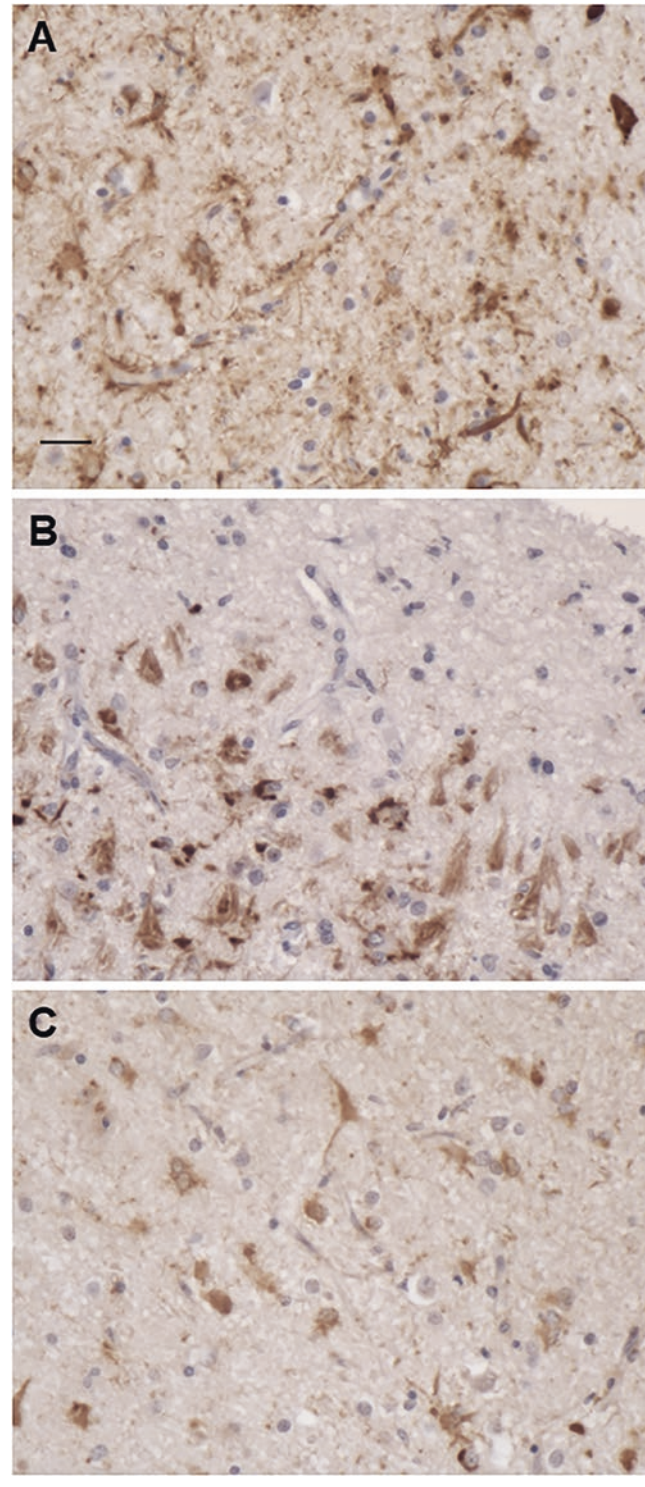

Fig. 14 Tau pathology in the temporal cortex of a patient (ex-boxer) with chronic traumatic encephalopathy. Tau inclusions in nerve cells and glia adjacent to small blood vessels labelled with anti-tau antibodies AT8 (**a**), RD3 (**b**) and RD4 (**c**). Scale bar, 25 μm

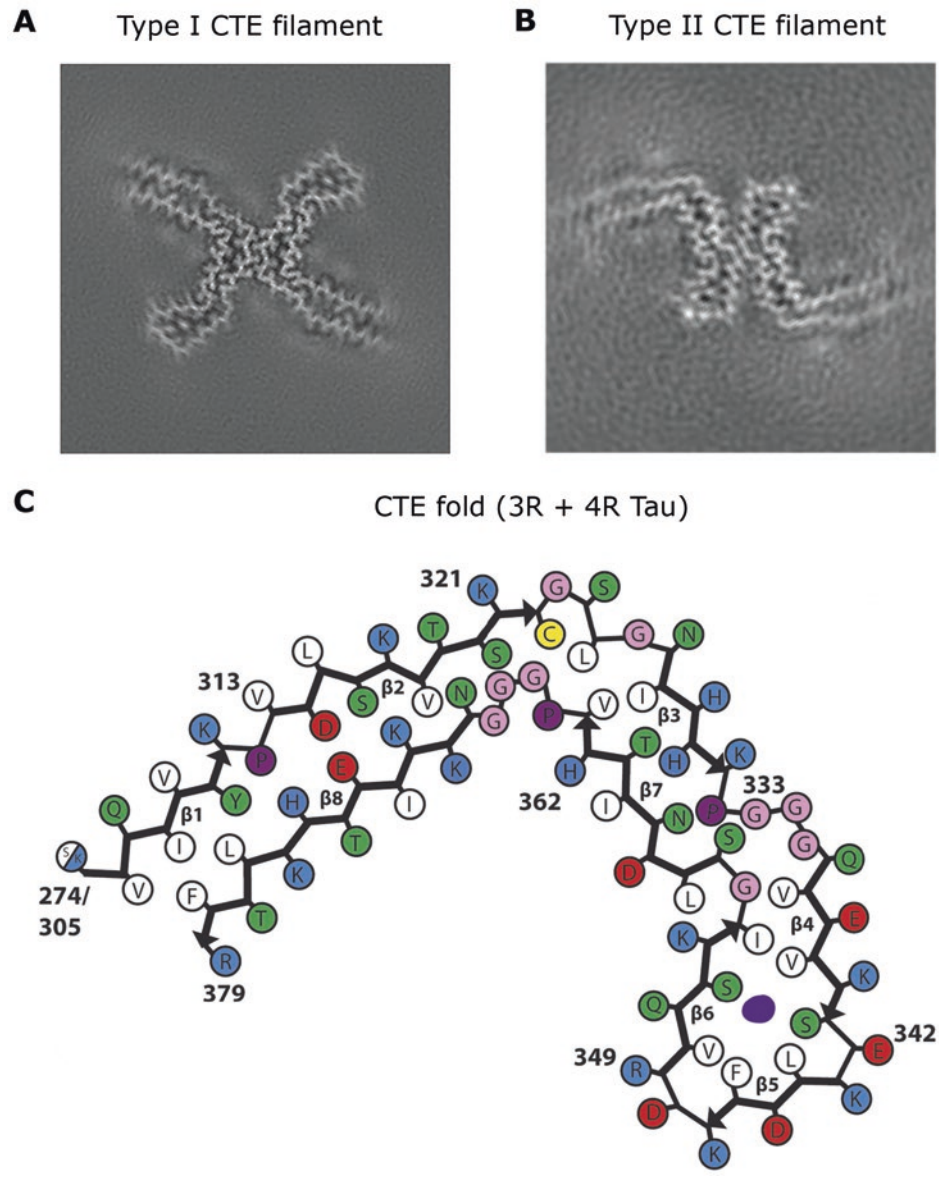

Fig. 15 Structures of tau filaments from chronic traumatic encephalopathy. Type I and Type II tau filaments are characteristic, with Type I filaments forming the vast majority. (**a**, **b**), Unsharpened cryo-EM densities of Type I (**a**) and Type II (**b**) filaments. The Type I filament was resolved to 2.3 Å and the Type II filament to 3.4 Å. Both filament types show identical pairs of protofilaments. They differ in their inter-protofilament packing (ultrastructural polymorphs). In CTE Type I filaments, protofilaments pack through an anti-parallel steric zipper formed by residues ^{324}SLGNIH^{329}. The interface in CTE Type II filaments comprises residues ^{332}PGGGQ^{336}. (**c**), Schematic view of the tau protofilament core of CTE. The observed eight β-strands (β1–β8) are shown as arrows. The central non-proteinaceous density is shown in violet

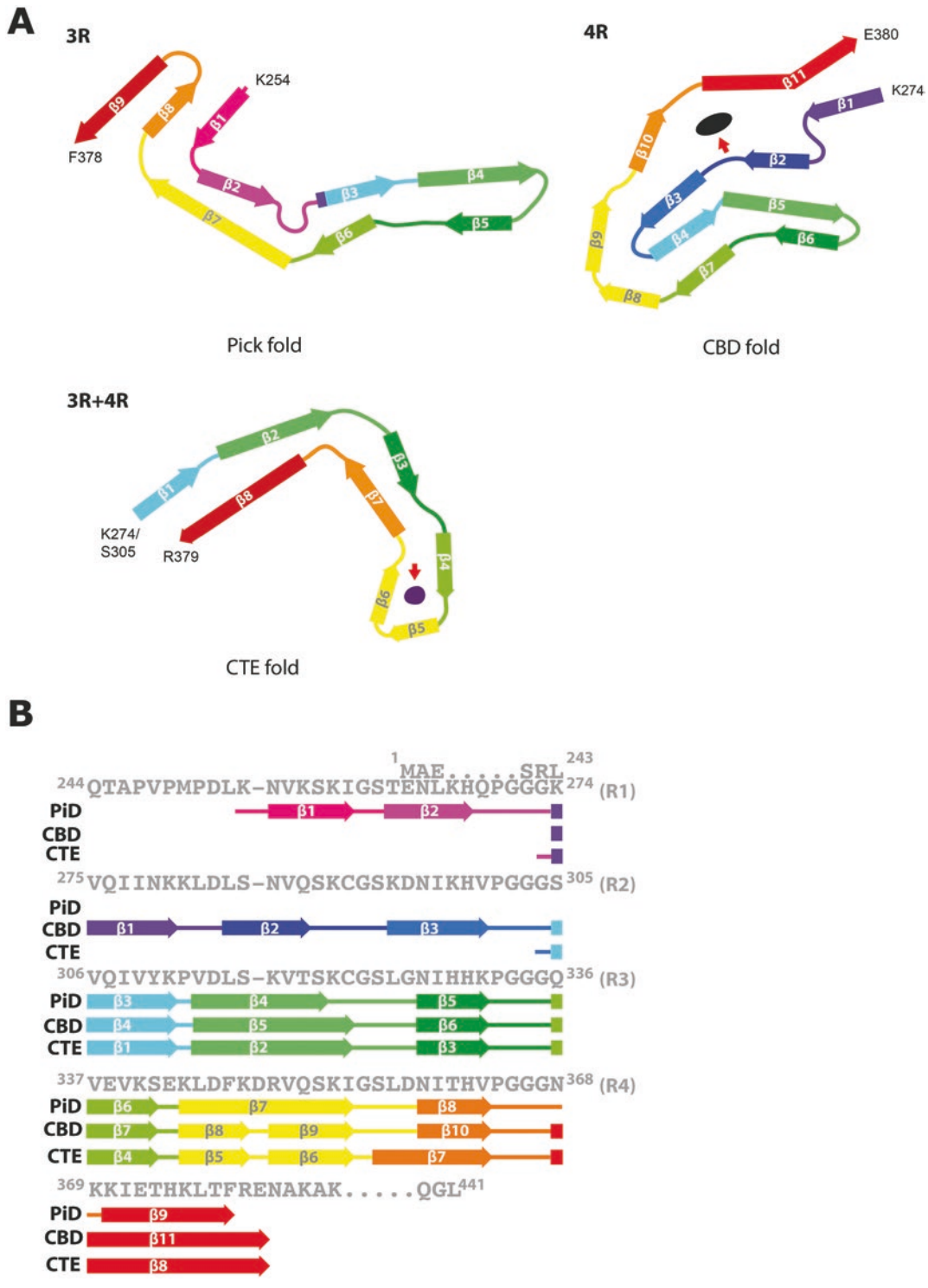

Fig. 16 Structures of tau filament cores from human brain. (**a**) Protofilament from Pick's disease (Pick fold), a 3R tauopathy; protofilament from corticobasal degeneration (CBD fold), a 4R tauopathy; protofilament from chronic traumatic encephalopathy (CTE fold), a 3R + 4R tauopathy. Red arrows point to the internal densities in CBD and CTE folds. β-Strands are marked by thick arrows (11 in the CBD fold, 9 in the Pick fold and 8 in the CTE fold). (**b**), Schematic depicting the microtubule-binding repeats (R1-R4) of tau and the sequence after R4, with β-strands found in the cores of tau filaments marked by thick arrows. Colours of individual β-strands are the same in (**a**) and (**b**)

cides with an opening up of the C-shape, and a reversal in the orientation of residues S356 and L357. In CTE Type I filaments, two identical protofilaments pack in a staggered manner through an anti-parallel steric zipper formed by residues ^{324}SLGNIH^{329}. The interface in CTE Type II filaments is also staggered and comprises the same residues as the interface in Alzheimer's disease–paired helical filaments (^{332}PGGGQ^{336}), but a kinked conformation reduces the number of hydrogen bonds across the interface.

The above-mentioned findings establish CTE as different from Alzheimer's disease, even though tau inclusions of both diseases are made of all six brain isoforms. In contrast to Alzheimer's disease, CTE is also characterised by an abundant glial tau pathology. The presence of a single CTE tau fold implies that the glial and neuronal tau inclusions are made of the same protofilament. The presence of identical CTE tau folds in the brains of a former American footballer and two ex-boxers establishes the presence of the same disease.

Conclusion

Assembled tau protein has been known to form the filamentous inclusions of a number of frontotemporal dementias since the 1980s. The finding that the same protein can be found in the inclusions of multiple diseases led some to conclude that the formation of tau inclusions is an epiphenomenon of little significance. The identification of mutations in *MAPT* in FTDP-17 T changed all that. To date, 65 disease-causing mutations have been identified. Most are missense mutations, but some change the ratio of 3R/4R tau. Clinicopathological studies have shown links between some mutations in *MAPT* and sporadic tauopathies.

Ongoing work has shown that the structures of tau filaments from sporadic PiD, CBD and CTE are different. Thus, the same protein takes on distinct structures in different diseases (Fig. 16). So far, in individuals with the same disease, be it PiD, CBD or CTE, filament structures were identical. It remains to be seen how the structures of tau filaments from the brains of individuals with *MAPT* mutations compare to each other and to those from sporadic diseases.

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Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathological Subtypes: Clinical and Mechanistic Significance

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Introduction

Frontotemporal dementia (FTD) is a heterogeneous clinical syndrome, characterized by progressive changes in behavior, personality, and/or language, with relative preservation of memory [1]. Major clinical subtypes include the behavioral-variant FTD (bvFTD) and two forms of primary progressive aphasia (PPA); the nonfluent/agrammatic and semantic variants (nfvPPA and svPPA, respectively). In addition, FTD is often associated with motor features, either an extrapyramidal movement disorder (atypical parkinsonism or corticobasal syndrome—CBS) or motor neuron disease (MND; usually classical amyotrophic lateral sclerosis—ALS). A family history is present in 25–50% of cases, with autosomal dominant FTD caused by mutations in several different genes [2].

The neuropathology underlying clinical FTD is also heterogeneous. Relatively selective degeneration of the frontal and temporal lobes is a consistent feature and "frontotemporal lobar degeneration" (FTLD) is used as the generic term for those pathologies that commonly present as clinical FTD [3, 4]. As with many other neurodegenerative conditions, the pathology of most cases of FTD includes the abnormal intracellular aggregation and accumulation of some pathological protein(s). Until quite recently, the vast majority of FTLD cases fell into two broad categories—those characterized by cellular inclusions composed of the microtubule-associated protein tau (FTLD-tau) and those with tau-negative inclusions that could only be detected with immunohistochemistry (IHC) against the nonspecific marker of pathological protein accumulation, ubiquitin (FTLD-U) [5]. In 2006, two publications each described three distinct patterns of FTLD-U pathology, based on the anatomical distribution and morphology of ubiquitin immunoreactive (-ir) neuronal inclusions in the cerebral cortex

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[6, 7]. Importantly, the pathological features that defined each of the subtypes in these two independent studies were almost identical, providing powerful validation of the results. The significance and legitimacy of the pathological subtypes were further supported by the finding of relatively specific correlations with different clinical phenotypes [6] and with the subsequent recognition that most of the newly identified genetic causes of FTD were each consistently associated with a specific type of FTLD-U pathology, including a novel (fourth) pattern that is only found in cases caused by mutations in the valosin-containing protein gene (*VCP*) [8–10]. A major breakthrough occurred, later in 2006, when the transactive response DNA-binding protein with M_r 43 kD (TDP-43) was identified as the ubiquitinated pathological protein in most cases of FTLD-U (which now became FTLD-TDP) and in sporadic ALS, strengthening the concept that FTD and ALS are closely related conditions with overlapping pathogenesis [11, 12]. Subsequent studies confirmed TDP-43 as the pathological protein in most clinical and genetic subtypes of FTLD-U, and the same criteria were adopted for the pathological subclassification of FTLD-TDP, with only minor modifications [13–15].

Over the past decade, the concept and utility of the current FTLD-TDP subtyping system has gained wide acceptance and has been repeatedly validated through its application in new case series and by the discovery of additional clinical, genetic, and pathological correlations. Moreover, recent studies have demonstrated that cases with each of the different pathological subtypes are associated with different genetic risk factors, and that the insoluble protein extracted from postmortem brain tissue has differing physical and biochemical properties [16–18]. These findings suggest that accurate pathological subtyping of cases and a better understanding of their biochemical basis will likely be important to advance the development of biomarkers and targeted therapies for FTD.

Major Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathological Subtypes

Although the studies that originally described the FTLD-U subtypes-evaluated ubiquitin-ir pathology in neocortex, hippocampus, and (in one study) striatum [6, 7], the diagnostic criteria that are now commonly used to subclassify FTLD-TDP cases are based exclusively on neocortical features (Table 1). Several studies have shown that these criteria are equally applicable and give comparable results regardless of whether the antibody used recognizes phosphorylated or phosphorylation-independent TDP-43 [15, 19]. The two discordant numbering systems introduced in the original papers have since been replaced with the harmonized alphabetic classification that is used later in the chapter [20].

Neocortical Features

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type A

Type A cases are characterized by abundant TDP-43-ir neuronal cytoplasmic inclusions (NCIs) and short thick dystrophic neurites (DN), which are concentrated in the superficial cortical layers (Fig. 1). The NCIs are mostly compact (cNCIs) and have an oval or crescentic shape. Lentiform neuronal intranuclear inclusions (NIIs) are also usually present, but they are much less abundant.

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type B

Type B cases have at least moderate numbers of NCI in both superficial and deep cortical layers, with relatively few DN and no NII. Most of the NCIs have a diffuse granular morphology (dNCI), sometimes referred to as "pre-inclusions." Importantly, some cases also have a background of delicate and small,TDP-43-ir threads and dots (ThD), which, when concentrated in layer II, may

Table 1 FTLD-TDP subtypes: distinguishing pathological features*, associated phenotypes, and causal mutations

	Type A	Type B	Type C	Type D
TDP-ir pathology				
Neocortex	II: cNCI, DN, NII	II-VI: dNCI	II-VI: long DN	II-VI:DN, NII
Hippocampus	den: NII CA1: threads	den: dNCI	den: cNCI	
Subcortical	WM: threads BG: DN, NII SN: DN	WM: GCI BG: dNCI, GCI SN: dNCI, GCI LMN: NCI	BG: cNCI	BG: DN, NII SN: DN, NII
Phenotypes	bvFTD, nfvPPA	bvFTD, nfvPPA, ALS	svPPA	IBMPFD, ALS
Mutations	*GRN* *C9orf72, TBK1*	*C9orf72, TBK1*		*VCP*

*See main text for full description of regional pathology. *II* cortical lamina II; *II–VI* cortical laminae II to VI; *ALS* amyotrophic lateral sclerosis; *BG* basal ganglia; *bvFTD* behavioral variant frontotemporal dementia; *C9orf72* chromosome 9 open reading frame 72 gene; *CA1* cornu ammonis region 1; *cNCI* compact neuronal cytoplasmic inclusions; *den* dentate lamina of hippocampus; *DN* dystrophic neurites (short unless otherwise specified); *dNCI* diffuse NCI; *GCI* glial cytoplasmic inclusions; *GRN* granulin gene; *IBMPFD* inclusion body myopathy with Paget disease of bone and frontotemporal dementia; *LMN* lower motor neurons; *NII* neuronal intranuclear inclusions; *nfvPPA* non-fluent-variant primary progressive aphasia; *SN* substantia nigra; *svPPA* semantic variant PPA; *TBK1* TANK binding kinase 1 gene; *TDP-ir* TDP-43 immunoreactive; *VCP* valosin containing protein gene; *WM* white matter

resemble the superficial laminar distribution that is typical of type A cases; however, this ThD pathology is neither consistent nor specific for type B cases.

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type C

Type C cases have a predominance of DN with few, if any, NCI and no NII. DNs are somewhat more abundant in superficial cortical layers, and many have a unique long, tortuous morphology.

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type D

The characteristic feature of FTLD-TDP type D pathology is an abundance of lentiform NII and delicate short DN, which are somewhat concentrated in superficial laminae. cNCI are rare in this subtype.

Hippocampal and Subcortical Pathology

In addition to the characteristic neocortical features, most cases of FTLD-TDP are also found to have significant TDP-43-ir pathology in limbic and subcortical anatomical regions (Table 1) [8, 21, 22]. Although not included in the diagnostic criteria, each of the neocortical subtypes shows a highly consistent pattern of subcortical involvement, which may be helpful when classifying difficult cases, and which may help to explain the range of associated clinical features [22].

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type A

A highly characteristic feature of type A cases is the presence of delicate TDP-43-ir threads in hippocampal CA1 region, which is often associated with significant pyramidal cell loss (hippocampal sclerosis) (Fig. 1). Type A cases also tend to have abundant white matter threads, a predominance of DN in subcortical grey matter regions, and small numbers of NIIs in the hippocampus and striatum. Diffuse and compact NCIs are also present in the hippocampal dentate and striatum, but they tend to be less abundant than in type B or C cases.

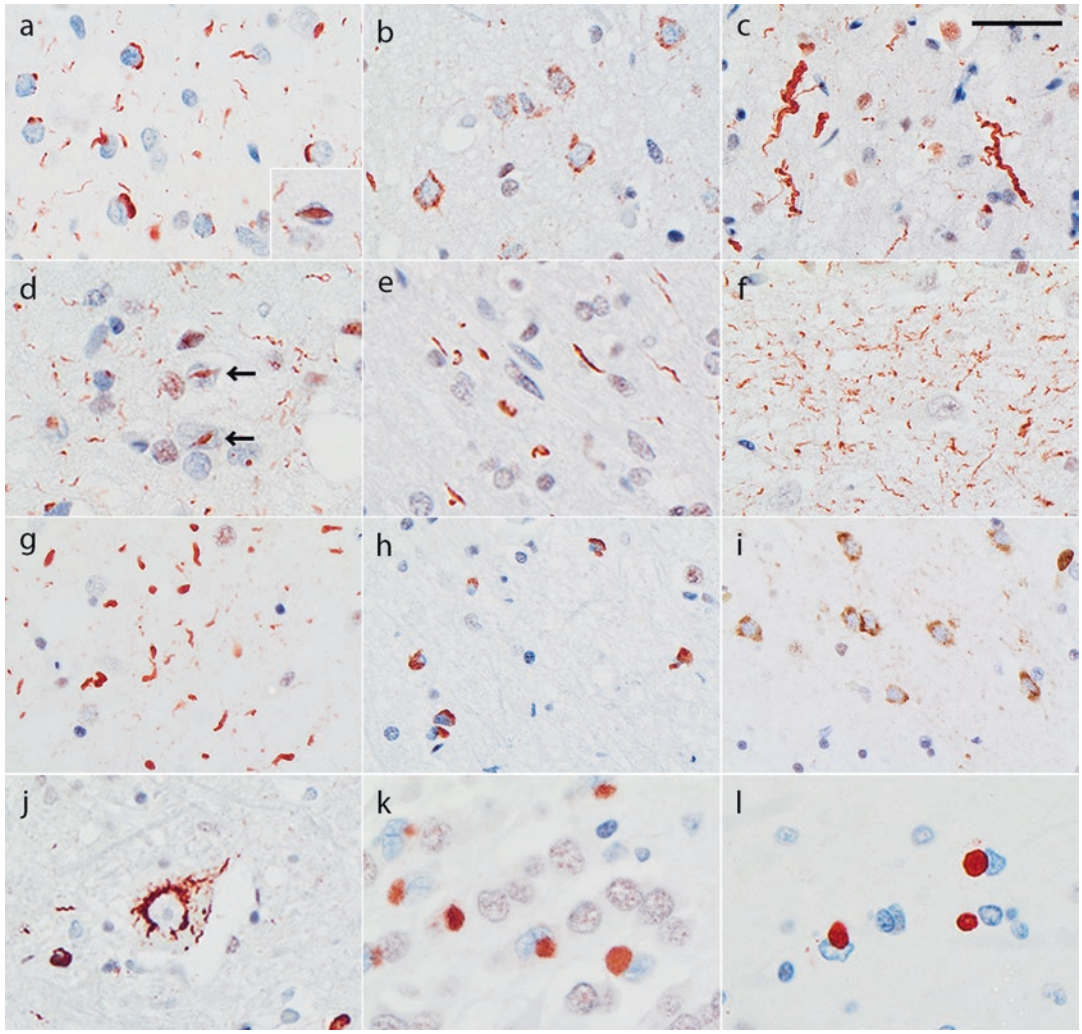

Fig. 1 TDP-43 immunoreactive pathology in different FTLD-TDP subtypes. Subtypes are defined by the pattern in the neocortex: type A has compact neuronal cytoplasmic inclusions (cNCIs), short dystrophic neurites (DNs), and some lentiform neuronal intranuclear inclusions (NIIs, insert) concentrated in layer II (**a**); type B has diffuse granular NCIs (dNCIs) throughout the neocortex (**b**); type C has DNs, many of which are long and tortuous DNs (**c**), and type D has numerous NIIs (arrows) and delicate short DNs (**d**). Each subtype also shows a characteristic pattern of pathology in the hippocampus and subcortical regions. Type A cases have thread pathology in the subcortical white matter (**e**), delicate wispy threads in hippocampal CA1 (**f**), and a predominance of DN and occasional NII in striatum and other subcortical grey matter regions (**g**). Type B cases have glial cytoplasmic inclusions in the subcortical white matter (**h**), a predominance of dNCI in subcortical grey matter (**i**), and NCI in lower motor neurons of the medulla and spinal cord (**j**). Type C cases have compact "Pick body-like" NCI in dentate granule cells of the hippocampus (**k**) and striatum (**l**). Bar: 40 µm (**a**–**c**, **f**–**j**), 10 µm (**a**, insert), 30 µm (**d**, **e**, **l**), 25 µm (**k**). TDP-43 immunohistochemistry

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type B

The most defining subcortical feature of type B cases is frequent NCI in lower motor neurons (LMN) of the hypoglossal nucleus and spinal cord, which may have diffuse, compact, or filamentous morphology. Moderate numbers of TDP-43-ir glial cytoplasmic inclusions (GCIs) are present in the cerebral white matter. Many

subcortical gray matter regions have abundant NCIs, which are predominantly diffuse, with more modest numbers of GCI.

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type C

The hippocampal dentate gyrus and striatum consistently show numerous cNCIs that have a unique "Pick body-like" morphology with uniform solid consistency and smooth round contour (in contrast to the cNCI found in some type A and type B cases, which usually appeared as a compact aggregate of coarse granules). The cerebral white matter is not involved, and most other subcortical structures show only occasional DN.

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type D

Modest numbers of DN and NII are present in the amygdala, basal ganglia, nucleus basalis, thalamus, and midbrain. The pons, medulla, and cerebellum are consistently spared. Notably, the dentate granule cells of the hippocampus are free of NCI.

Clinical Correlations

There is significant overlap in the clinical features associated with each of the different major protein classes of FTLD (FTLD-tau, FTLD-TDP, and FTLD-FET) and among the subtypes within each class [1, 23–25]. Moreover, in cases within all the pathological groups, a patient's phenotype often evolves as their disease progresses to include additional clinical features. In general, cases of svPPA and FTD combined with ALS are usually found to have underlying FTLD-TDP pathology; those with nfvPPA or prominent extrapyramidal features (particularly sporadic cases) more often have FTLD-tau, whereas bvFTD can be associated with any of the FTLD pathologies. Within the FTLD-TDP group, each of the subtypes shows a number of important clinical correlations.

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type A

Most cases present with features of bvFTD, often with prominent apathy and social withdrawal. An aphasic presentation is less common and may be nfvPPA or more difficult to classify. Executive dysfunction and some degree of memory impairment are not uncommon, particularly with older age at presentation. Neuropsychiatric manifestations (delusions, hallucinations, or obsessive behaviors) are particularly common in those with an underlying *GRN* or *C9orf72* mutation. Extrapyramidal features are reported in up to half of the cases but are rarely the presenting or predominant feature, whereas ALS is highly unusual.

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type B

This pathology underlies the vast majority of cases in which FTD occurs in combination with clinical features of ALS. The presenting dementia syndrome is most often bvFTD, while language problems usually develop later. Psychosis is particularly common in those caused by the *C9orf72* repeat expansion, where they may be the presenting feature in one-third [26]. Extrapyramidal features develop in at least half.

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type C

There is a particularly strong correlation between this pathology and svPPA, with most cases of clinical svPPA having FTLD-TDP type C pathology. There are often some associated behavioral changes, and cases with predominant *right* temporal involvement may present with loss of sympathy/empathy, hyposexuality, prosopagnosia, and obsessive/compulsive behavior. Psychiatric features and extrapyramidal movement disorders are much less common than with the other subtypes. Although these cases do not develop ALS, they may have some upper motor neuron features. Patients with this pathology also tend to have a

slower disease progression and older age at death compared to those with the other FTLD-TDP subtypes.

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Type D

This pathology is exclusively found in familial cases with *VCP* mutations in which there is variable penetrance of inclusion body myopathy (90%), Paget disease of bone (45%), FTD (30%), and ALS (10%) [27]. The FTD syndrome is usually bvFTD, with language dysfunction and extrapyramidal motor features being relatively uncommon.

Genetic Correlations

Patients with FTD due to mutations in *GRN* are consistently found to have FTLD-TDP type A pathology at autopsy [10, 13, 15], while those with *VCP* mutations always have type D (Table 1) [8, 28]. In contrast, the *C9orf72* repeat expansion has more variable TDP-43-ir pathology, with most studies reporting some cases with type A and others with type B FTLD-TDP [26, 29–32]. Moreover, two recent studies found that only half of *C9orf72* mutation cases had either typical type A or type B pathology, while the largest group had the combined pathological features of both type A and type B (type A + B, see later) [15, 22]. Although there are currently few reports describing the pathology in cases of FTD caused by mutations in the TANK-binding kinase 1 gene (*TBK1*), these also seem to include both type A and type B cases [33–36]. There are a number of other rare genetic causes of FTD that have been reported to have TDP-43 pathology but for which there is currently insufficient information to define the specific pattern (e.g., *TARDBP*, *CHCHD10*, *OPTN*, *SQSTM1*) [2]. Finally, in addition to causal mutations, genetic risk factors have been identified for FTLD-TDP, some of which are associated with a specific pathological subtype (e.g., a variant in *UNC13A* was found to be associated with FTLD-TDP type B cases but not A or C) [17].

Other Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Subtypes and Patterns of Pathology

Although the subtyping of FTLD-TDP cases has proven to be useful and the current criteria generally accepted, several reports have identified cases that are difficult to classify, either because the pattern of pathology does not to fit with any of the existing subtypes or because it shows overlapping features of more than one subtype [15, 22, 37–42]. Although these cases represent a small minority in most series, they highlight some of the technical and interpretive differences that exist among neuropathologists in applying the current FTLD-TDP classification criteria.

Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Cases with Overlapping Pathological Features

In a series of 30 FTLD-TDP cases selected for a BrainNet Europe study, an initial panel of five neuropathologists designated three cases as "atypical" type B, four cases as having features of both type A and type B (A + B), and two cases that had insufficient TDP-43 pathology for typing [37]. A follow-up analysis of this case series, involving a much larger group of investigators, found relatively poor agreement among the reviewers in assigning FTLD-TDP subtypes (~62%), with the worst agreement observed for FTLD-TDP type B cases. However, agreement was better (up to 85%) when raters were asked to simply dichotomize between types A or B and type C, suggesting that the major difficulty was in differentiating between type A and type B. An earlier study by Armstrong et al., that used principal component analysis, and that included a combination of TDP-43-ir pathology and additional changes that are not part of the standard subtyping criteria (neuronal loss, neuronal enlargement, neuropil vacuolation, oligodendroglial inclusions) also found significant over-

lap among FTLD-TDP subtypes, particularly between type A and type B [43]. Finally, a small series of four cases of FTD with delusions also reported two as having mixed type A + B pathology and two which were unclassifiable [39]. Importantly, all four of these cases harbored the *C9orf72* repeat expansion.

The issue of combined subtypes was addressed more specifically in a study designed to compare the pathological features that define the subtypes, based on the original ubiquitin-based criteria versus TDP-43 IHC [15]. In this series of 78 FTLD-TDP cases, the majority (81%) were easily classified as types A, B, or C; however, 15 cases demonstrated mixed features of both FTLD-TDP type A and type B. These mixed cases were characterized by NII, NCI, and short DN in layer II (type A features), as well as granular NCI in deeper neocortical layers that were at least as numerous as in layer II (type B features) (Fig. 2). Importantly, 12 of the 15 type A + B cases carried the *C9orf72* repeat expansion, while the remaining three cases had clinical or pathologic evidence of MND. In fact, half of the *C9orf72* mutation cases in this study had FTLD-TDP type A + B pathology, while the other half were classified as pure type B.

A similar analysis of 89 cases by another group found that a higher proportion of cases (96%) could be readily subtyped as A, B, or C, whereas five cases were judged to have features that crossed FTLD-TDP subtypes, all of which also had concomitant MND pathology [44]. One case with the *C9orf72* mutation exhibited type B features with NII (type A + B), while another *C9orf72* case exhibited a mixed type B + C pattern. The other three were non-*C9orf72* cases and included one type C with NII (type A + C), and two type B with long DN (type B + C).

Although the current subtyping criteria are based solely on pathological findings in neocortical sections, each of the different FTLD-TDP subtypes has also been reported to be associated with distinctive patterns of TDP-43 pathology in limbic and subcortical regions (see above) [21, 22]. In a recent study, Mackenzie and Neumann investigated whether including pathological data from subcortical anatomical regions would allow for better classification of cases with a mixed pattern of neocortical TDP-43-ir pathology [22]. Using standard observational assessment of neocortical sections, all of the non-*C9orf72* mutation cases could be readily classified as type A, B or C, and these results were validated using non-biased hierarchical clustering analysis (HCA). Furthermore, HCA of the pathological data from subcortical regions found that these cases again formed three distinct clusters, which perfectly matched the neocortical type A, B, and C groups. In contrast, using the neocortical data, only half of the *C9orf72* mutation cases clustered with either the type A or type B cases, and the remaining 14 formed a distinct cluster exhibiting mixed features of type A and type B. When the same group of *C9orf72* mutation cases was analyzed using the limbic and subcortical TDP-43 pathology data, more of the cases segregated as type A or type B; however, five cases remained as a separate mixed A + B cluster.

The results of these studies indicate that, although the vast majority of FTLD-TDP cases can be readily subclassified, based on the current criteria, there exists a minority that are difficult to assign because they have a combination of pathological features that characterize more than one subtype. Interestingly, these mixed patterns of pathology seem to be particularly common in cases with the *C9orf72* repeat expansion and sporadic cases that have features of both FTD and ALS [15, 22, 39, 41, 44], suggesting that there may be something unique about the mechanism of TDP-43 mis-metabolism in these clinical and genetic groups that result in greater pathological heterogeneity.

Novel Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Subtypes

In 2017, Lee et al. described a series of seven cases that were difficult to categorize, based on the 2011 harmonized FTLD-TDP classification,

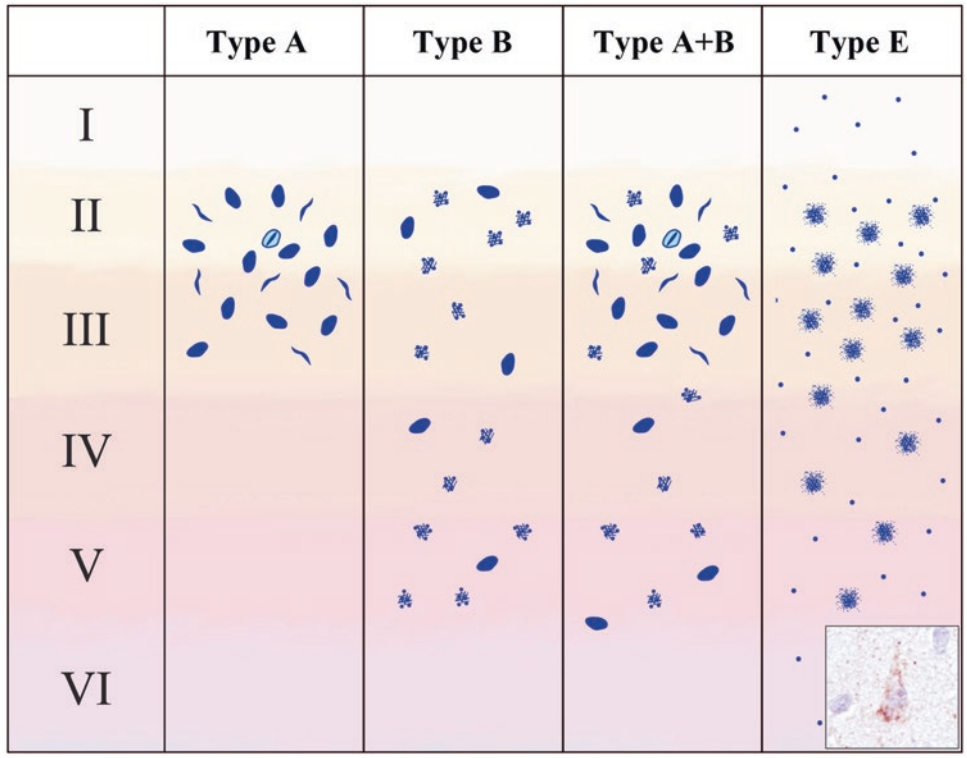

Fig. 2 Schematic representation of TDP-43 inclusion morphologies and distribution in cases with mixed (A + B) and novel (E) subtypes. Type A + B cases show the characteristic features of type A (compact neuronal cytoplasmic inclusions (NCI), short dystrophic neurites, and neuronal intranuclear inclusions, concentrated in layer II), as well as the characteristic features of type B (compact and diffuse granular NCI in deep and superficial layers). Type E cases exhibit granulofilamentous neuronal cytoplasmic inclusions and a background of and fine grains (inset photo) throughout the neocortex. (Modified from Lee et al. 2017 [40])

that they felt represented a unique subtype, which they designated as type E [40]. The neocortical TDP-43 pathology involved all cortical layers and consisted of weakly staining granulofilamentous neuronal cytoplasmic inclusions (GFNIs) set in a background of very fine grain-like deposits (Fig. 2). In contrast to the NCI found in other FTLD-TDP subtypes, these GFNIs were negative for ubiquitin and mostly negative for p62. GFNI and grain pathology, as well as TDP-43-ir oligodendroglial inclusions, were also present in a wide range of neocortical and subcortical regions, sparing only of the occipital neocortex and cerebellum. Motor neuron involvement was a consistent feature, although only one case was associated with clinical features of ALS. Interestingly, these FTLD-TDP type E cases were consistently associated with a rapid clinical course of 1–3 years' duration.

Some additional reports have described cases with pathology similarity to the type E of Lee et al. Takeuchi et al. reported a subset of sporadic ALS cases with NCI, granular or dot like DN, and a high density of GCI, involving motor cortex, other neocortical regions, basal ganglia, and spinal cord [41]. Ubiquitin and p62 IHC were not performed. The authors interpreted these findings as distinct from FTLD-TDP types A–D. More recently, two cases with 1-year duration of PPA and ALS were reported to exhibit FTLD-TDP type E pathology, consisting of TDP-43-ir, p62-negative GFNI, and grains [42]. Finally, a case of rapidly progressive Foix-Chavany-Marie syndrome (FCMS) has been reported to exhibit FTLD-TDP type E [45]. FCMS,

also known as bilateral opercular syndrome, is characterized by prominent motor dysfunction, involving muscles of the face, tongue, and pharynx. While the etiology of FCMS is diverse, sometimes being associated with bilateral opercular infarcts, progressive forms of FCMS share clinical similarities to FTD [46].

While FTLD-TDP type E may represent a distinct subtype, the association with ALS, in some cases, and the similarities with the pathological features of type B cases, raise the possibility that types E and B represent a continuum. Indeed, FTLD-TDP type B has been described as often having a predominance of granular rather than compact NCIs, a synaptic pattern of neuropil inclusions, and abundant threads and dots [15, 21, 32]. Given the relatively short disease duration of most cases with FTLD-TDP type E, one possibility is that these represent "early-stage" disease when the TDP-43 inclusions are still immature and have not yet coalesced into a more typical FTLD-TDP type B morphology and become ubiquitinated. Alternatively, FTLD-TDP type E could represent a more virulent pathology, which spreads through the brain and spinal cord quickly, resulting in rapid clinical disease progression and relatively immature inclusions.

Unique Patterns of TDP-43 Pathology in Rare Disorders

Unique patterns of TDP-43 proteinopathy have been described in a few rare neurodegenerative diseases, not typically classified as FTLD or ALS. A screen of non-neurodegenerative disease neuropathology specimens revealed that Rosenthal fibers and eosinophilic granular bodies, which may be present in reactive gliosis and in some low-grade astrocytic brain tumors, label with TDP-43 IHC [47]. Rosenthal fibers are protein aggregates within astrocytes that are composed primarily of glial fibrillary acidic protein (GFAP) and are also the defining pathological feature of Alexander disease, a leukodystrophy associated with *GFAP* mutations [48]. A subsequent study demonstrated that Rosenthal fibers in Alexander disease are also TDP-43-ir [49]. Thus, Alexander disease represents a unique TDP-43 proteinopathy, in which neurodegeneration is associated exclusively with astrocytic inclusions.

Another unique pattern of TDP-43 proteinopathy is found in Perry syndrome, a progressive neurodegenerative disease characterized by parkinsonism, psychiatric symptoms, and hypoventilation, caused by mutations in the gene encoding dynactin-1 (*DCTN1*) [50]. In addition to modest numbers of NCI composed of the dynactin subunit p50, cases of Perry syndrome exhibit TDP-43-ir NCI, DN, oligodendroglial GCI, axonal spheroids, and perivascular astrocytic inclusions [51]. Based on the very limited number of cases reported ($n = 3$), the pattern of TDP-43 pathology in Perry syndrome seems to be distinct from FTLD-TDP, with a predisposition for the substantia nigra and other subcortical regions with only mild and inconsistent involvement of the cerebral cortex.

In both Alexander disease and Perry syndrome, TDP-43 protein aggregation is likely secondary to the accumulation and dysfunction of other proteins (GFAP and dynactin, respectively). Nonetheless, these conditions are informative by demonstrating that TDP-43 proteinopathy may result from diverse mechanisms.

TDP-43 Pathology in Aging and Common Neurodegenerative Disorders

Finally, it is important to recognize that some degree of TDP-43-ir pathology is a common finding in the limbic structures of the mesial temporal lobe in aging and in association with many common neurodegenerative disorders, including Alzheimer's disease and Lewy body disease [52]. The clinical relevance of this pathology and its relationship to FTLD-TDP is currently the topic of tremendous interest and controversy [53, 54], but it is beyond the scope of this chapter.

Biochemical Basis of Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Subtypes

Biochemical Properties of TDP-43 Aggregates and Disease-Associated Modifications

Aggregated TDP-43 isolated from human postmortem FTLD-TDP brain tissue is poorly detergent soluble and subject to a variety of disease-associated posttranslational modifications (PTMs). These result in a highly characteristic biochemical banding pattern by immunoblot analysis, with the presence of disease-specific bands of ~25 kDa, ~45 kDa, and a high molecular smear, in addition to the ~43 kDa band corresponding to normal TDP-43 (Fig. 3a) [11, 12]. PTM of TDP-43 include N-terminal truncation, phosphorylation, ubiquitination, acetylation, cysteine oxidation, and sumoylation [55]. The characterization of the various PTMs and their functional consequences are still poorly understood and not fully validated in human postmortem tissue; however, there is increasing evidence that TDP-43 PTM may play a crucial role in disease pathogenesis, and that modulation of disease-relevant PTM might be a promising avenue for future therapeutic approaches.

N-Terminal Truncation and C-Terminal Fragments

The presence of short TDP-43 fragments of ~25 kDa is a hallmark feature of FTLD-TDP [11, 12]. They are composed of N-terminally truncated TDP-43 species as demonstrated by absent labeling with antibodies raised against the N-terminus (amino acids 6–24) but detection with antibodies against the extreme C-terminus of TDP-43 [56]. N-terminal sequencing of fragments isolated from human postmortem tissue has revealed arginine at position 208 [57], and mass spectrometry analysis of tryptic digests of isolated fragments has demonstrated aspartic acid residues at positions 219 and 247 [58] as potential cleavage sites. Although these experiments clearly demonstrate that these short species contain N-terminally truncated fragments that extend to the extreme C-terminus, it is still unclear whether they all include the entire C-terminal region. Moreover, the origins and pathomechanistic relevance of the C-terminal

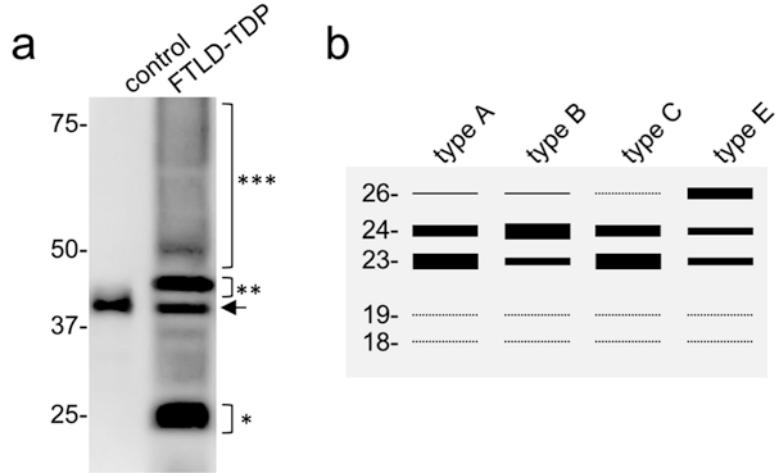

Fig. 3 Immunoblot analysis of sarcosyl-insoluble protein fractions from FTLD-TDP shows the disease-specific biochemical signature of TDP-43 with pathological bands −25 kDa (*), −45 kDa (**), and a high molecular smear (***), in addition to the physiological TDP-43 band (arrow) also present in control brains (**a**). Schematic representation of distinct banding patterns of C-terminal fragments among FTLD-TDP subtypes (types A, B, and C based on Kawakami et al. 2018; type E based on Lee et al. 2017) [40, 84] (**b**)

fragments (CTFs) remain to be fully established. Most studies propose proteolytic cleavage/degradation by caspases [59, 60], asparaginyl endopeptidase [61], or calpains [62]; although other explanations include alternative splicing events or usage of alternate translational start sites [63, 64]. However, several proposed cleavage sites and generated fragments/isoforms in these studies do not match well with the fragments observed in human postmortem tissue, suggesting that additional enzymes and/or mechanisms might exist.

The potential role of TDP-43 CTF in disease pathogenesis is supported by findings of cellular toxicity upon overexpression of CTF in some cellular and animal models [57, 65]; however, in several other model systems, the correlation is less clear [66]. Moreover, while enrichment for CTF over full-length TDP-43 is a characteristic feature of most types of cellular inclusions in the cerebral cortex, CTFs are less abundant or absent in inclusions in spinal cord LMN in FTLD-TDP/ALS [56] and in cortical pre-inclusions [67], thereby suggesting that the formation of CTF might not be mandatory for aggregation and toxicity.

Phosphorylation

Aberrant phosphorylation of TDP-43 has been recognized as one of the major PTMs of pathological TDP-43 since its initial discovery as the disease protein in FTLD-TDP and ALS [11, 12]. The fact that the majority of pathogenic *TARDBP* mutations either introduce or disrupt potential serine/threonine phosphorylation sites or introduce phosphomimic residues (glutamate/aspartate) suggest that alterations in the phosphorylation status of TDP-43 play a crucial role in the pathogenesis of TDP-43 proteinopathies [55]. TDP-43 has 41 serine, 15 threonine, and 8 tyrosine residues acting as potential phosphorylation sites. Mass spectrometry analysis of recombinant TDP-43 treated with casein kinase 1 and of aggregated TDP-43 isolated from human postmortem tissue has revealed several phosphorylated residues [68–70]; however, so far, only five sites at the C-terminus of TDP-43 (pS379, pS403, pS404, pS409, pS410) have been validated in pathological TDP-43 inclusions in human postmortem tissue with phosphorylation-site-specific antibodies [19, 68]. Phosphorylation at these C-terminal serine residues (with pS409/410 as most studied sites) is a highly consistent and specific feature of aggregated TDP-43 in all types of pathological TDP-43 inclusions, in all sporadic and familial FTLD-TDP subtypes, and is considered an abnormal event due to the lack of phosphorylation of these sites under physiological conditions [15, 19, 68, 70, 71]. The functional consequences of TDP-43 C-terminal phosphorylation are not fully resolved. While some experimental studies have described an association with decreased solubility of TDP-43 and greater toxicity [68, 72], others have reported the opposite effects with phosphomimicking mutants showing increased solubility and reduced toxicity [73, 74]. Further insights into the role of TDP-43 phosphorylation, in regulating its physiological functions (e.g., RNA binding, dimerization) and the impact of abnormal phosphorylation events through the identification of the involved kinases and phosphatases, will be crucial steps to elucidate the pathological processes in TDP-proteinopathies.

Ubiquitination

Ubiquitination of TDP-43 aggregates is a key feature in FTLD-TDP; however, insights into the specific lysin residues that are ubiquitinated in human FTLD-TDP tissues and the functional consequences are still limited. The detection of TDP-43 Lys-48- and Lys-63-linked polyubiquitin chains in cellular models is suggestive of proteasomal and autophagosomal degradation of TDP-43 [75]. Lysine residues 84, 95, 102, 114, 121, 140, 145, 160, 176, 181, and 263 have been identified as ubiquitinated TDP-43 residues in cellular models, however, with some variability among studies, most likely reflecting the complexity of ubiquitin-proteasome regulation of TDP-43 in a highly context-dependent manner [76–79]. Notably, ubiquitination of lysin 84 has been postulated as an important modifier of nuclear import of TDP-43 in mutagenesis experiments, and a complex interplay between TDP-43 ubiquitination at distinct sites and phosphoryla-

tion at pS409/410 has been observed [77]. However, validation of any ubiquitination site in human postmortem FTLD-TDP tissue is lacking, and, to date, the only ubiquitinated residue identified by mass spectrometry of insoluble protein extracts from postmortem tissue (of an ALS patient) is lysine 79 [80].

Acetylation

Another modification of lysine residue is acetylation. So far, two acetylation sites have been identified in cellular models at lysine 145 (located in RRM1) and lysine 192 (located in RRM2) [81]. However, since mutation of TDP-43 at these two sites did not completely abrogate acetylation, additional acetylated lysine residues may be present. Acetylation at lysine 145 and lysine 192 has been shown to impair the binding of TDP-43 to RNA and to promote TDP-43 phosphorylation at pS409/410 [81]. The potential role of this modification in disease was demonstrated using an antibody specific for TDP-43 acetylated at lysine 145, which revealed acetylated TDP-43 as a biochemical component of the TDP-43 inclusions in ALS/FTD spinal cord, which are known to be composed of the full-length protein, but not the inclusions in cerebral cortex, which are composed primarily of CTFs that lack the epitope recognized by the antibody [81].

Sumoylation

Evidence for sumoylation of TDP-43 comes mainly from a proteomics approach that revealed SUMO-2/3 in complex with insoluble TDP-43 in a cellular model system overexpressing a CTF [75]; however, sumoylation of TDP-43 has not yet been directly demonstrated in human disease tissue.

Cysteine Oxidation

Upon exposure to oxidative stressors, TDP-43 has been reported to undergo cysteine oxidation and disulfide cross-linking in vitro and in cellular models, resulting in enhanced TDP-43 aggregation and alterations in subcellular distribution [82]. TDP-43 has six cysteine residues, and there is experimental evidence that all sites contribute to proper folding, self-assembly, and oligomerization of TDP-43 [55]. While increased levels of cross-linked TDP-43 species are present in FTLD-TDP brains [82], the pathomechanistic role of cysteine oxidation and cross-linking remains to be fully determined.

Biochemical Diversity of TDP-43 Aggregates in Frontotemporal Lobar Degeneration TDP-43-Immunoreactive Pathology Subtypes and Evidence for TDP-43 Strains

A crucial open question in the FTLD-TDP research field is the molecular basis behind the huge clinical and neuropathological phenotypic variability, as well as the selective vulnerability in FTLD-TDP subtypes and ALS. The concept that distinct self-propagating conformers of an aggregated protein (“strains”) represent the basis for phenotypic diversity in a neurodegenerative disease was first established in prion diseases [83]. By analogy, a popular hypothesis to explain the heterogeneity in FTLD-TDP is the presence of different conformational types of misfolded TDP-43 (“TDP-43 strains”) that can propagate in a prion-like manner [84]. In fact, there is a growing body of evidence supporting this idea.

Biochemical heterogeneity of aggregated TDP-43 has already been recognized in the initial report on the discovery of TDP-43 as the disease protein [11]. Briefly, monoclonal antibodies (clones 182 and 406) generated against insoluble protein fractions from FTLD-TDP brains, each labeled distinct bands of the N-terminally truncated TDP-43 species by immunoblot, specific for either type A or type B FTLD-TDP cases (then referred to as FTLD-U type 3 or type 1, respectively). This suggested that each antibody was recognizing either a specific conformation or a specific pattern of PTM of aggregated TDP-43 species, each being specific for a different FTLD-TDP subtype. Several studies have been performed since then to further characterize and correlate an immunoblot banding pattern of TDP-43 CTF with distinct FTLD-TDP subtypes, with most employing antibodies against pS409/410 [19, 40, 68, 85]. Using high-

percentage polyacrylamide gel electrophoresis, distinct CTF with up to three major bands (23 kDa, 24 kDa, and 26 kDa) and two minor bands (18 kDa and 19 kDa) can be present in sarkosyl-insoluble lysates of FTLD-TDP brains, with some studies demonstrating subtle differences in the banding pattern among FTLD-TDP subtypes (Fig. 3b) [40, 68, 85]. Briefly, in type A, the most intense major band is at 23 kDa; in type B, it is at 24 kDa; type C lacks the 26 kDa band and has a more prominent 23 kDa band; and type E shows three major bands with the most intense at 26 kDa. However, significant variability within and overlap between subtypes exists [19]; so, the biochemical classification of subtypes remains challenging, and more sensitive methods of detection, quantification, and analysis of various CTFs and their PTMs are required.

Nevertheless, it is tempting to speculate that the different banding patterns in FTLD-TDP may correspond to different conformational species of abnormal TDP-43. In strong support of this idea, protease treatment of insoluble TDP-43 aggregates has revealed different patterns of protease-resistant cores among FTLD-TDP subtypes, highly suggestive of different conformers [18]. More recently, a new extraction method, termed "SarkoSpin," has been developed that allows extraction of pathological TDP-43 species from postmortem tissue with improved separation from physiological TDP-43, compared to the previous sequential extraction protocols [16]. This approach has revealed additional insights into distinct biophysical properties of aggregated TDP-43 among the TDP-43 proteinopathies, with TDP-43 from FTLD-TDP type C found to exhibit a higher intrinsic density and protease-resistant CTF core compared to that from cases of type A or ALS (type B not examined).

In addition to the observed biochemical/structural differences, crucial support for the idea that distinct pathological TDP-43 species may (at least partially) explain the clinical and pathological variability in FTLD-TDP comes from the observations that TDP-43 extracted from different FTLD-TDP subtypes exhibits different levels of seeding activity and toxicity in vitro and in vivo. The first such evidence was provided by Nokanko et al. who reported that seeding activity of TDP-43 extracted from human postmortem tissue in a cell culture model was more efficient when using extracts from type A and type B cases compared to type C [86]. Interestingly, the banding pattern of insoluble CTF extracted from the seeded cell lysates resembled that from the corresponding FTLD-TDP subject used as the seed, suggestive of a prion-like self-templating process of TDP-43 aggregation. These results were validated and expanded in a report where TDP-43 aggregates extracted using the SarkoSpin protocol from FTLD-TDP type A cases demonstrated templated seeding and toxicity in cultured primary neurons, while those from subtype C seemed inert [16]. While in these studies no differences between sporadic and genetic cases were mentioned, Porta et al. reported that lysates from *GRN* mutation carriers had the highest seeding activity in their cellular screening assay, followed by *C9orf72* mutation carriers and sporadic FTLD-TDP type A and type B cases [87]. Biochemical analyses of the lysates revealed a correlation between the presence of two minor CTF bands of 18 kDa and 19 kDa and seeding activity, suggesting that distinct fragments and/or conformational TDP-43 species seem to be more potent [87]. Most importantly, this study provided the first in vivo evidence for propagation of TDP-43 pathology in a prion-like manner by demonstrating the induction and spreading of de novo TDP-43 pathology, following the intracerebral injection of FTLD-TDP aggregates isolated from human FTLD-TDP type A tissue into transgenic mice expressing cytoplasmic human TDP-43 and non-transgenic mice [87].

Therefore, current insights are consistent with the idea that the progression of FTLD-TDP pathology involves self-templating seeded aggregation and cell-to-cell spreading of pathological TDP-43 that exists in different conformations. However, more extensive biochemical, biophysical, and seeding studies are needed to strengthen the hypothesis that different TDP-43 conformers/species, indeed, contribute to the phenotypic heterogeneity in FTLD-TDP patients (e.g., by demonstrating whether distinct FTLD-TDP subtype-derived TDP-43 aggregates can repro-

duce their distinct clinical and neuropathological characteristics in animal models).

Finally, in addition to biochemical differences of TDP-43 itself, co-aggregation of other proteins into TDP-43 inclusions might contribute to the diversity among FTLD-TDP subtypes. This hypothesis is supported by double-label immunohistochemical findings with co-localization of hnRNP E2 and TDP-43 in FTLD-TDP subtype C and subsets of FTLD-TDP type A inclusions, but not in type B cases [88, 89]. However, in-depth biochemical characterization of the protein composition of TDP-43 inclusions is required to further address this.

Summary

The current criteria for the pathological subclassification of FTLD-TDP are widely accepted and show a number of highly relevant clinical and genetic associations. However, the presence of a small proportion of cases with novel patterns of TDP-43-ir pathology indicates the need for additional correlative studies. Investigations, to date, suggest that the basis for the different subtypes is, at least partially, biochemical and/or conformational variation in the aggregating protein. Further studies to more fully elucidate the nature of the subtype-specific pathological species of TDP-43 will be crucial to the development of useful biomarkers and targeted therapies.

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Lysosomal Dysfunction and Other Pathomechanisms in FTLD: Evidence from Progranulin Genetics and Biology

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Introduction

Frontotemporal lobar degeneration (FTLD) is a complex disease, characterized by progressive degeneration of frontal and temporal lobes and extensive neuroinflammation, which manifests with a range of clinical disorders and inevitably leads to death [1]. The most common clinical presentation is behavioral variant frontotemporal dementia (bvFTD) characterized by progressive deterioration of personality, social behavior with disinhibition, and cognition [2]. However, in other FTLD patients, language dysfunction in the form of primary progressive aphasia is the predominant feature [3]. FTLD spectrum disorders are a leading cause of early-onset dementia with most patients presenting first symptoms around 60 years of age; however, a range from 25 to 90 years has been reported [4]. Importantly, more than 40% of FTLD patients have a positive family history of FTLD or related neurodegenerative disorders, sometimes with an autosomal dominant pattern of inheritance, which speaks to the strong genetic component of the disease [5–7].

In 1998, mutations in the microtubule-associated protein tau gene (*MAPT*) were identified as the first genetic cause of FTLD in a set of families with bvFTD and parkinsonism [8–10]. The subsequent identification of several FTLD families that lacked mutations or rearrangements in *MAPT*, despite genetic linkage to the same chromosomal region, suggested the presence of another genetic cause for FTLD close to the *MAPT* locus on chromosome 17q21 [11]. Intriguingly, these families also had pathology distinct from the *MAPT* carriers: they showed pathological inclusions positive for ubiquitin but negative for the tau protein. This remained a conundrum in the field until 2006 when systematic sequencing of candidate genes in a 6 Mb critical region, defined by the linked families, led to the identification of heterozygous progranulin gene (*GRN*) mutations as the second cause of autosomal dominant FTLD [12, 13]. In the same year, the TAR DNA-binding protein 43 (TDP-43) was found to be the main component of the ubiquitin inclusions in the *GRN* families, and FTLD with TDP-43 pathology (FTLD-TDP) was discovered to be the most common type of FTLD pathology [14, 15]. We now know that *GRN*

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mutation carriers always present with FTLD-TDP type A, a specific FTLD-TDP subtype defined based on the distribution, cellular localization, and shape of the TDP-43 inclusions [16].

Progranulin (PGRN), encoded by *GRN*, is a conserved 593-amino-acid secreted glycoprotein. It has an unusual structure with seven full-length and one half-length granulin domains connected by linker regions and can be proteolytically cleaved to release individual 6 kDa granulin peptides [17] (Fig. 1). Multiple proteases are able to generate granulins from PGRN including neutrophil elastase [18, 19], proteinase 3 (a neutrophil protease) [19], matrix metalloproteinase 12 (MMP-12) [20], MMP-14 [21], and a disintegrin and metalloproteinase with thrombospondin motifs 7 (ADAMTS-7) [22]. On the other hand, PGRN can be stabilized from proteolysis by secretory leukocyte protease inhibitor (SLPI). Notably, in vitro assays showed that the cleavage of PGRN by proteases does not always result in the release of solely 6–12 kDa granulin fragments; instead, multiple intermediate-sized granulin products are also produced [18–20].

PGRN is highly expressed in epithelial cells such as those in the intestinal crypt, skin, kidney, and reproductive tracts, as well as immune cells within the lymphoid tissue of the lung, gut, and

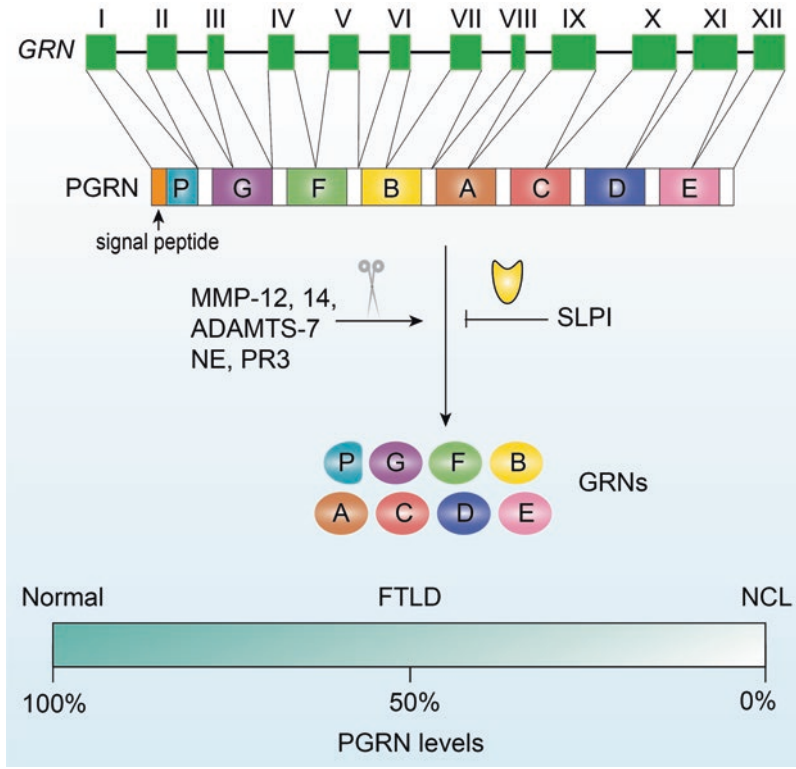

Fig. 1 PGRN, granulins, and associated disease phenotypes. Schematic of a part of the genomic structure of the progranulin gene (*GRN*) with 12 coding exons represented by green boxes. Following mRNA transcription and translation, the precursor protein progranulin (PGRN) is generated consisting of a signal-peptide, seven full-length granulin domains (granulins G, F, B, A, C, D, E) and one half-length granulin domain (granulin P). PGRN can be further cleaved by multiple enzymes to generate individual granulins. The cleavage of PGRN can be inhibited through its binding to secretory leukocyte protease inhibitor (SLPI). Heterozygous loss-of-function *GRN* mutations which reduce PGRN levels to 50% of normal levels cause frontotemporal lobar degeneration (FTLD), whereas homozygous loss-of-function *GRN* mutations with no residual PGRN expression cause neuronal ceroid lipofuscinosis (NCL). *NE* neutrophil elastase; *PR3* proteinase 3; *MMP* matrix metalloproteinase; *ADAMTS-7* a disintegrin and metalloproteinase with thrombospondin motifs 7

spleen [23, 24]. In the brain, PGRN is mainly expressed in microglia and in different types of neurons including Purkinje cells, hippocampus pyramidal cells, and cerebral cortical neurons [23, 25, 26]. Both PGRN and granulins have been implicated in diverse functional processes. Specifically, early work focused on the role of PGRN in cell cycle progression and cell migration in a range of tissue remodeling processes including development, wound repair/inflammation, and tumorigenesis [27]. It was later determined that PGRN and one of the granulins, granulin E, exhibited neurotrophic properties [28] and most recently PGRN and granulins were shown to act as a key regulator of lysosomal health [29]. How *GRN* mutations affect these various biological processes and which mechanism is most important for the development and progression of FTLD remains an area of active investigation.

In this chapter, we briefly summarize the *GRN* mutational spectrum and its associated phenotypes, followed by an in-depth discussion on possible *GRN*-related disease mechanisms with emphasis on the recent evidence implicating PGRN and granulins in lysosomal function and dysfunction.

PGRN Mutational Spectrum and Associated Phenotypes

Heterozygous Loss-of-Function Mutations in *GRN* Cause FTLD

Through sequencing studies in FTLD and early-onset dementia populations, *GRN* mutations are now estimated to account for 5–20% of patients with a positive family history and 1–5% of apparently sporadic FTLD patients [30]. Mutations are mostly small insertions, deletions, or duplications affecting the *GRN* reading frame, splice-site mutations, or nonsense mutations, all leading to a premature termination codon and degradation of the mutant *GRN* mRNA transcript through nonsense-mediated decay. Larger partial or complete gene deletions have also been reported [31–33]. Mutations affecting the signal-peptide sequence of PGRN, such as p.W7R and p.A9D, are also considered pathogenic because these mutants are unable to recruit the signal recognition particle, preventing secretion, leading to degradation of mutant *GRN* mRNA [34–36]. Two recent international studies summarized the different *GRN* mutations and number of families reported, showing at least 140 different loss-of-function mutations in more than 400 unrelated families (more families were reported by Moore et al., but genomic information was not used to determine cryptic relationships) [4, 37]. The most common mutation is c.813_816del (p.T272Sfs*10), with hundreds of affected patients from a founder population in Italy [38]. Other common mutations include c.1477C > T (p.R493*), c.709-1G > A (p.?), and c.26C > (p.A9D), all of which are more geographically distributed [4].

FTLD patients are heterozygous carriers; thus, a loss of 50% PGRN is the uniform consequence of all known pathogenic mutations resulting in PGRN haploinsufficiency. Because PGRN is a secreted protein, the reduction in PGRN can be detected in plasma or cerebrospinal fluid (CSF) samples from *GRN* mutation carriers and used as a diagnostic biomarker [39–42]. Together with in vitro functional assays, these PGRN measurements in human biofluids have also proven useful in the study of *GRN* missense variants which were identified through routine screening of FTLD patients but for which the pathogenicity is less obvious [35, 43–45]. For a select few missense mutations (including p.C105R, p.C139R, and p.C521Y affecting critical conserved cysteine residues), compelling evidence has now been gathered to support an effect on PGRN; however, most of these mutations do not completely eliminate PGRN expression and/or function and thus may represent FTLD risk factors rather than clear pathogenic mutations. The notion that a partial loss of PGRN (resulting in less than 100% but more than 50% remaining expression) could function as an FTLD risk factor is already demonstrated by rs5848, a common variant in the 3' untranslated region of *GRN* which was first described as a risk factor for FTLD-TDP in 2008 and was shown to partially reduce PGRN

expression [46]. A highly significant association of this variant with risk to develop FTLD-TDP type A (indistinguishable from the pathology seen in *GRN* mutation carriers) was recently confirmed in a large international study [47]. Interestingly, this same variant has been implicated in other neurodegenerative disorders, including Alzheimer's disease (AD) and hippocampal sclerosis of aging, which may point to the fact that a partial loss of PGRN leads to a general increase in neurodegenerative disease risk [48–51].

Homozygous Loss-of-Function Mutations in *GRN* Cause Neuronal Ceroid Lipofuscinosis

Unexpectedly, homozygous loss-of-function mutations in *GRN* were reported in 2012 as the cause of neuronal ceroid lipofuscinosis (NCL) type 11 [52]. NCLs are neurodegenerative disorders characterized by the accumulation of abnormal lipopigment in lysosomes and clinical features of (usually) childhood-onset visual failure, cerebellar ataxia, seizures, and progressive decline in cognitive and motor functions [53]. The discovery of homozygous *GRN* mutations in patients with a lysosomal storage disorder marked a landmark finding providing novel and strong evidence for a functional role of PGRN within lysosomes. To date, eight different families with a total of 11 homozygous *GRN* mutation carriers have been reported (summarized in [54]). Strikingly, while most patients presented with classical NCL symptoms with a juvenile onset, three patients developed behavioral and cognitive symptoms that would allow the diagnosis of probable bvFTD [2], with one patient only developing symptoms at 56 years of age. This suggests that FTLD and NCL are extreme phenotypes on a spectrum with as yet unknown factors contributing to the phenotypic presentation. Residual expression of PGRN in homozygous *GRN* mutation carriers, as a result of hypomorphic variants that still synthesize some PGRN, may explain the bvFTD phenotype in some patients, but other factors likely play a role. Importantly, neuropathological examination in one patient homozygous for *GRN* mutations showed typical hallmarks of neuronal ceroid lipofuscinosis but no TDP-43 inclusions similar to those observed in FTLD [54].

Genetic Modifiers of FTLD-*GRN*

The large variability in age at disease onset among pathogenic *GRN* mutation carriers, even within single families [55], recently prompted an unbiased two-stage genome-wide association study using more than 400 patients from unrelated *GRN* families [37]. No genome-wide significant association with age at onset was identified. However, when symptomatic *GRN* carriers were compared to healthy individuals (in an attempt to identify possible protective factors), a genome-wide significant association was reported for genetic variants at the *TMEM106B* locus (rs1990622) and the *GFRA2* locus (rs36196656). These findings imply that even pathogenic *GRN* mutations are not fully penetrant and provide hope that TMEM106B-related and/or GFRA2-related pathways might be future targets for treatments for FTLD. The current biological knowledge on these candidate proteins in relation to PGRN is discussed in sections "PGRN Neurotrophic Receptors and Signaling Pathways" (GFRA2) and "Lessons from TMEM106B". (TMEM106B).

PGRN Deficiency Leads to a Loss of Neurotrophic Support

Neurotrophic Effect of PGRN and Granulins

Before the link of PGRN with FTLD, its function in cell growth had been extensively studied in the cancer biology field. Increased expression of PGRN was reported in several types of cancer including liver, breast, kidney, prostate, and ovarian cancer and was found to be associated with poor prognosis (for review, see [56, 57]). In vitro studies found PGRN functions as a growth factor. Treatment with PGRN induced cell proliferation

[58, 59] and prevented the apoptosis of tumor cells [18, 60–63]. In vivo, a reduction in PGRN expression greatly reduced tumor formation [64–67].

Prompted by the discovery of *GRN* mutations in FTLD patients, it was subsequently shown that PGRN was able to regulate survival and neurite outgrowth of different types of neurons. Primary cultured cortical and hippocampal neurons derived from *Grn*$^{-/-}$ mice showed deficits in neurite outgrowth and branching, significantly reduced neuronal survival, and increased caspase-mediated apoptosis [68, 69]. PGRN knockdown in NSC-34 motor neurons and human neural cells, differentiated from NHNP cells (a human neural progenitor cell line), also significantly reduced survival [70, 71], whereas PGRN-deficient hippocampal slices were susceptible to glucose deprivation [72]. On the other hand, either overexpression of PGRN or treatment with recombinant PGRN protein increased neurite outgrowth and the survival of primary cortical, hippocampal, and motor neurons [28, 70, 73]. Moreover, in vivo studies using zebrafish showed that PGRN knockdown decreased axonal outgrowth inducing motor neuron deficits, which could be rescued by overexpression of PGRN [74, 75]. Interestingly, overexpression of human PGRN mRNA also rescued human TDP-43-induced axon growth deficits in zebrafish [76].

It is known that PGRN can be cleaved into mature ~6 kDa granulin peptides as well as intermediate-length cleavage products (as mentioned in the introduction). Whereas the function of intermediate progranulin products in this context remains to be determined, diverse effects of granulins have been reported. Granulin A was shown to either induce cell growth or inhibit cell proliferation in different cell lines, while granulin B presented with inhibitory or antagonistic effects to granulin A [77–79]. Granulin D has been shown to regulate DNA synthesis in cultured astrocytes and glioblastoma cells [80]. Granulins C and E have also been shown to have neurotrophic properties. In hippocampal neurons, granulin C was shown to have comparable neurotrophic effects to granulin E [69], whereas in another study in primary motor neurons and cortical neurons, granulin E but not granulin C had an effect [81]. Moreover, granulin AaE (equivalent to human granulin E in zebrafish) was shown to promote the survival of neuronal cells in zebrafish [82]. Interestingly, deletion of granulin E from PGRN completely abolished the neurotrophic effect of PGRN suggesting that granulin E may be the key domain or region involved in the neurotrophic effect of PGRN [82]. In line with these findings, inhibition of PGRN processing (by SLPI) abolishes PGRN-enhanced survival and neurite outgrowth in cortical neurons [28].

PGRN Neurotrophic Receptors and Signaling Pathways

In both cancer cells and primary neurons, PGRN has been shown to stimulate cell proliferation and promote cell survival through the activation of typical growth factor signal transduction pathways such as extracellular regulated kinase (ERK1/2) and the phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt) cell survival pathways [59, 60, 68, 83–87]. One study revealed that PGRN treatment stimulated the phosphorylation of glycogen synthase kinase-3 beta (GSK-3β) in cultured neurons and knockdown of PGRN in SH-SY5Y cells impaired retinoic acid-induced differentiation and reduced the level of phosphorylated GSK-3β [73]. In addition, loss of PGRN in a human neural progenitor cell line led to an increase in Wnt/β-catenin signaling [71]. The involvement of a wide range of signaling cascades suggests PGRN might function through different neurotrophic receptors. However, thus far, the nature of the neurotrophic receptor(s) in the CNS remains unclear.

Sortilin (SORT1), a member of the vacuolar protein sorting 10 protein (VPS10P) domain receptor family [88], is one of the best-studied cell receptors for PGRN. Like PGRN, SORT1 is highly expressed in neurons in the frontal cortex, one of the most vulnerable brain regions in FTLD-*GRN*, and SORT1 also has a high binding affinity to PGRN [89]. SORT1 is known to be involved in the trafficking and signaling of several neuro-

trophins [90]. For instance, SORT1, forming a receptor complex with the common neurotrophin receptor (p75NTR), binds to the pro-form of nerve growth factor-β (proNGF) and triggers cell death signaling [91]. However, SORT1 solely functions as a sorting receptor for PGRN [89]. Indeed, multiple studies have shown the neurotrophic effect of PGRN and granulins is independent of SORT1. Either pharmacologic inhibition of the granulin E-SORT1 interaction or deletion of the SORT1 binding site of granulin E failed to abolish the neurotrophic function of granulin E [81]. In support of this notion, knockout or knockdown of SORT1 in mouse and zebrafish does not cause axonal outgrowth defects [81], and loss of SORT1 fails to abrogate the neurotrophic effect of PGRN in cultured neurons [69].

What about other candidate neurotrophic receptors? By using an unbiased antibody-based screen for differential tyrosine phosphorylation levels of 49 different human receptor tyrosine kinases, Neill et al. recently found that PGRN rapidly increased tyrosine phosphorylation of ephrin type A receptor 2 (EphA2) in a human urinary bladder carcinoma cell line [92]. PGRN binds to EphA2 with an affinity comparable to SORT1 (both of them are around the nanomolar range) [89]. PGRN binds to EphA2 on the cell surface and activates both mitogen-activated protein kinase and Akt and promotes capillary morphogenesis (Fig. 2). Separately, proteomic analysis of transgenic mice with inducible neuronal PGRN overexpression predicted activation of Notch signaling pathways in this model [93], and additional experiments confirmed that PGRN can bind to all four Notch receptors through the extracellular domain. PGRN also co-localized with Notch1 in primary dorsal root ganglia (DRG) neurons. Interestingly, upon nerve injury, the expression of *Hey1* and *Hes* (two Notch target genes) increased in *Grn* overexpression and decreased in $Grn^{-/-}$ mouse DRG neurons compared to wild-type mice. These findings indicate that PGRN can activate Notch and EphA2 in the peripheral nervous system. Given the established survival support roles of EphA2 and Notch, further studies are warranted to determine if basal levels of PGRN activate EphA2 or Notch in the brain.

Finally, we recently identified genetic variants at the *GFRA2* locus as novel modifiers of the disease risk in FTLD patients carrying a *GRN* mutation [37]. GDNF family receptor alpha 2 (GFRA2) is a member of the glial cell line-derived neurotrophic factor (GDNF) receptor family and is known to function as the preferred receptor for neurturin (NRTN) [94]. GFRA2 binds with NRTN and further recruits and activates a transmembrane tyrosine kinase receptor known as RET, which can activate the mitogen-activated protein kinase (MAPK) and Akt signaling pathways (Fig. 2). The risk haplotype at the *GFRA2* locus is associated with lower mRNA levels of *GFRA2* in brain tissue as compared to the protective haplotype. Moreover, we determined that PGRN can directly interact with GFRA2 [37]. Notably, GFRA2 is also abundantly expressed in different brain regions, especially in the frontal cortex [37], a vulnerable brain region in FTLD-*GRN*. While more studies are needed, this work suggests that GFRA2 could potentially function as a signaling receptor for PGRN in the CNS and upregulation of GFRA2 could be considered as a therapeutic strategy.

Role of Inflammation in FTLD-*GRN*

Overview of PGRN and Inflammation

Although PGRN is widely expressed throughout the body, the expression of PGRN is enriched in the spleen and cells of the hematopoietic lineage, supporting the idea that PGRN is involved in the function and maintenance of the immune system. In particular, *GRN* expression is enriched in monocytes, dendritic cells, and granulocytes within the blood and microglia in the brain [95]. Further, early work isolated and identified peptide fragments of PGRN from inflammatory cells leading to speculation that PGRN may be involved in inflammation and wound healing [96].

Subsequent studies have found increased levels of PGRN in tissue and biofluids from many types of inflammatory states and conditions, ranging from bacterial and viral infections [97–101], insulin resistance and type 2 diabetes [102–

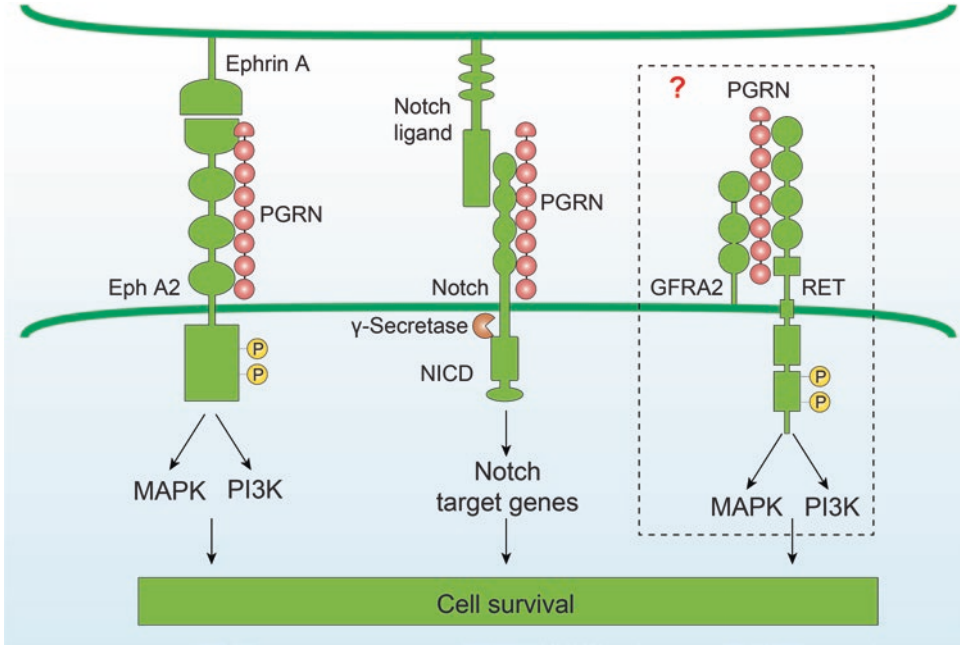

Fig. 2 Possible PGRN neurotrophic receptors and signaling pathways. Progranulin (PGRN) may bind to ephrin type A receptor 2 (EphA2) on the neuronal cell surface in the presence of ephrinA (from an adjacent cell) and activate its receptor tyrosine kinase, initiating neurotrophic signaling through MAPK/ERK and PI3K-Akt signaling pathways. PGRN might bind to Notch on the neuronal cell surface in the presence of Notch ligand (from adjacent cell) and trigger its cleavage to release the intracellular domain of the Notch protein (NICD), which then moves to the nucleus and increases the expression of genes involved in cell survival. PGRN might bind to GDNF family receptor alpha 2 (GFRA2) and further recruit and activate a transmembrane tyrosine kinase receptor RET, which can activate MAPK/ERK and PI3K-Akt signaling pathways. *MAPK* mitogen-activated protein kinase; *ERK* extracellular regulated kinase; *PI3K* phosphatidylinositol-3 kinase; *Akt* protein kinase B

104], liver dysfunction [105], and arthritis [106, 107]. Further, the *GRN* promoter has multiple binding sites for transcription factors related to inflammation, such as phorbol esters and multiple cytokines involved in the inflammatory response [108]. Indeed, treatment of murine embryo fibroblasts with interleukin-1 (IL-1) or tumor necrosis factor (TNF), two pro-inflammatory cytokines, leads to robust upregulation of *GRN* expression [109].

These observations led investigators to study whether the upregulation of PGRN was a consequence of inflammation or if PGRN can directly modulate inflammation. Work from the Bateman lab demonstrated that PGRN expression was upregulated during the wound response and PGRN likely functioned as a growth factor to facilitate wound healing [110]. In particular, they found that delivery of extracellular PGRN increased neutrophils, macrophages, fibroblasts, and blood vessel formation within the wound, leading them to conclude PGRN helped stimulate inflammation that is necessary for wound repair. Other labs, however, have found PGRN has the opposite effect in different models of inflammation. In 2002, PGRN (also called proepithelin or PEPI) was reported to have anti-inflammatory activity through blocking TNF activation of neutrophils [18]. In contrast, one of the granulins, granulin B (also called epithelin B), was pro-inflammatory in multiple assays. For example, granulin B inhibited proliferation of epithelial cells and induced the release of IL-8, a chemokine that attracts neutrophils. Work from Kessenbrock et al. found that application of recombinant PGRN can also reduced the influx of neutrophils following immune complex (IC)-stimulated inflammation in vivo [19].

Although some of these observations are conflicting, when considered together, these studies provide compelling evidence that PGRN expression is correlated with inflammation in different model systems and may play a modulatory role in inflammatory pathways. Nevertheless, the precise mechanism(s) how PGRN and granulins might mediate such pleiotropic effects on specific inflammatory cascades is much less clear. Future studies to understand the precise functions of PGRN and granulins will hopefully shine a light on these questions.

PGRN and Central Neuroinflammation

While early work focused on the role of PGRN on inflammation in peripheral tissues, the discovery of *GRN* mutations in FTLD prompted researchers to investigate whether PGRN was involved in inflammation in the central nervous system (CNS). PGRN is expressed in multiple neuronal populations as well as microglia throughout the brain [23, 111, 112], whereas astrocytes and oligodendrocytes do not appear to express PGRN at significant levels in vivo [113]. Multiple studies have discovered that the expression of PGRN by microglia is dramatically upregulated following an injury or other insults in animal models. For example, spinal cord injury [114], traumatic brain injury [115], injection of the neurotoxin quinolinic acid [116], or the endotoxin lipopolysaccharide [117] all activate microglia and lead to robust upregulation of *GRN* mRNA and PGRN protein. Most relevant to FTLD is the fact that PGRN levels are elevated across a wide variety of neurodegenerative diseases, which are often associated with neuroinflammation. Indeed, microglial PGRN itself is elevated in FTLD cases not caused by *GRN* mutations [118]. In contrast, FTLD cases with *GRN* mutations have reduced immunoreactivity for neuronal and microglia PGRN, supporting the idea that haploinsufficiency of PGRN and granulins extends to multiple cell types in the brain [119, 120]. In amyotrophic lateral sclerosis, PGRN expression is upregulated in the spinal cord, most likely due to activation of microglia [121]. Expression profiling of microglia from a mouse model of Creutzfeldt-Jakob disease (CJD) found increased levels of PGRN among a host of other genes involved in inflammation, interferon response, and complement pathways. Unbiased expression studies also identified changes in PGRN levels in multiple lysosomal storage disease models, likely driven by activated microglia [122].

Studies have also found increased PGRN expression in Alzheimer's disease (AD), which is especially relevant given the association of the *GRN* SNP rs5848 that decreases PGRN levels and increases the risk of developing AD [50, 51]. Increased immunoreactivity for PGRN in AD brain tissue labels activated microglia surrounding amyloid plaques as well as dystrophic neurites [13, 112, 113]. This observation extends to mouse models of AD where multiple groups have found increased levels of PGRN associated with amyloid plaques [123–125]. In clinical late-onset AD, higher CSF PGRN levels were associated with more advanced disease stages and cognitive impairment which was thought to reflect microglial activation during disease [126]. Importantly, a recent detailed immunohistochemical analysis of PGRN in AD brains replicated earlier findings that PGRN levels are increased with AD disease status but concluded that the increased PGRN signal is derived primarily from extracellular PGRN associated directly with amyloid beta (Aβ). Thus, further work is needed to understand the specific role of PGRN in AD pathology and pathogenesis [127].

Potential Mechanisms of Neuroinflammation in FILD-*GRN*

The clearest evidence that PGRN has an important role in central and peripheral inflammation comes from experiments examining the phenotype of *Grn*-deficient mice (reviewed in depth elsewhere) [57, 128]. Five unique $Grn^{-/-}$ and a novel $Grn^{R493X/R493X}$ knock-in mouse models have been developed thus far [72, 129–133]. All six models share a consistent age-dependent microgliosis and

astrogliosis throughout the brain including the cortex, hippocampus, and thalamus [133–136]. Moreover, macrophages and microglia isolated from *Grn*$^{-/-}$ *or* *Grn*$^{R493X/R493X}$ mice have an exacerbated inflammatory response when challenged with pro-inflammatory molecules [137–140]. Further, loss of PGRN leads to microglial upregulation of multiple lysosomal genes, increased production of cytokines and complement, and enhanced synaptic pruning by microglia in *Grn*$^{-/-}$ mice [138]. The authors suggest that PGRN may normally function as a "brake" to suppress aberrant activation of microglia during aging by facilitating proper phagocytosis and lysosome function. Taken together, it is clear that PGRN plays an important role in decreasing, or modulating, neuroinflammation; however, the precise mechanism(s) by which this is accomplished still needs further investigation. Next, we will examine a few possible mechanisms that could help explain how PGRN may modulate neuroinflammation and how loss of PGRN function contributes to FTLD pathogenesis.

PGRN Anti-inflammatory Activity Through Signaling

A key unresolved question is whether PGRN has inherent anti-inflammatory activity. It is well established that administration of exogenous PGRN has pleiotropic effects in cells, some of which can be considered anti-inflammatory. These observations led many investigators to search for PGRN receptors that may mediate these effects. In 2002, PGRN was reported to decrease inflammation through inhibition of TNF signaling in neutrophils, likely downstream after TNF binding to its receptors [18]. Subsequent work supported an anti-inflammatory effect of PGRN, potentially mediated through the TNF pathway. Extracellular PGRN was found to moderately reduce secretion of IL-8 from human aortic smooth muscle cells induced by TNF treatment [141]. In 2011, Tang et al. reported that PGRN bound directly to the TNF receptors (TNFRSF1A and TNFRSF1A) and functioned as a TNF antagonist [142]. Intriguingly, PGRN bound to TNFRSF1A and TNFRSF1A with a higher affinity compared to TNF, the known ligand. Further, recombinant PGRN was found to block TNF-induced inflammation in multiple cell culture assays and mouse models of TNF activity [142]. These results were initially greeted with excitement by the FTLD community because it might explain how decreased levels of PGRN lead to a pro-inflammatory state and ultimately set the stage for neurodegeneration. Unfortunately, following the original report, multiple pharmaceutical companies (*personal communication*) and academic labs have been unable to replicate the ability of PGRN to antagonize TNF binding or function [143–148]. The reasons for these discrepancies are unknown. Furthermore, from a broader perspective, it was never clear how an excess of TNF activity, theoretically caused by decreased levels of PGRN, could be the fundamental driver of either FTLD or NCL.

Although the potential anti-inflammatory activity of PGRN is fascinating, the preponderance of evidence suggests that it is unlikely to be mediated through antagonism of TNF activity. Alternatively, the binding of PGRN to other cell surface receptors may modulate inflammation. PGRN has been reported to bind directly, or indirectly, to a number of transmembrane receptors including delta homolog 1 (DLK1) [149], SORT1 [89], Toll-like receptor 9 (TLR9) [150], Notch1 [93], EphA2 [92], prosaposin (PSAP) mediated binding to the cation-independent mannose-6-phosphate receptor (M6PR), low-density lipoprotein receptor-related protein 1 (LRP1) [151], tyrosine-protein kinase receptor (Tyro3) [147], and GFRA2 [37]. Besides SORT1, most of these interactions have only been reported once and have not been extensively investigated, especially in the CNS. Moreover, the role of PGRN binding to any of these receptors and downstream effects on inflammation is speculative and needs to be validated and more thoroughly investigated.

The PGRN:Granulin Balance

Granulins are thought to be pro-inflammatory and could be another potential player in inflammation related to decreases in PGRN. The name "granulin" was derived from the fact that they were enriched in granules isolated from granulocytes and speculated to be cytokines [96].

Seminal work by Zhu et al. in 2002 found that PGRN could be cleaved in the extracellular space by elastase released from white blood cells, blocking PGRN's anti-inflammatory activity [18]. In contrast, the cleaved and released granulins reduced cell growth and produced a pro-inflammatory response. How might this observation be involved in FTLD? Some have speculated that the ratio of circulating PGRN to granulins is altered in FTD-*GRN* carriers leading to an imbalance, an increase in granulins, and subsequent inflammation. This idea has not been formally tested and awaits the development of antibodies specific to granulins, which is ongoing [120]. Although compelling, this hypothesis does not explain the even greater neurodegeneration and neuroinflammation that occurs in mice and humans completely deficient in PGRN and granulins [52, 54, 134, 152, 153]. Further, the precise pro-inflammatory mechanism for granulins, such as a signaling receptor, is unknown. Additionally, granulins have also been reported to have many beneficial effects, such as enhancing survival of motor neurons in culture [28], inducing neuronal outgrowth and branching [69], enhancing neuron survival and axon growth [154], and protecting retinal photoreceptor cell degeneration [155]. Finally, we, and other labs, have found that granulins are a common, endogenous protein produced in the lysosome of many cells [120, 156, 157]. This would suggest that granulins have a normal, homeostatic function inside the cell and aren't necessarily pro-inflammatory. In summary, granulins may play divergent roles depending on their location, and unraveling their function both inside of lysosomes and outside of the cell is an important focus of future research.

Contribution of Lysosomal Dysfunction in FTLD-*GRN*

Involvement of Lysosomal Dysfunction in FTLD-*GRN*

While the neurotrophic and anti-neuroinflammatory effects of PGRN have been well documented and studied for some time, recent evidence suggested a previously unrecognized but important function of PGRN within lysosomes. Firstly, although PGRN is a secreted protein, its main localization within the cells is in lysosomes [89, 114]. Moreover, at the transcriptional level, *GRN* is co-regulated with other lysosomal genes such as cathepsin D (*CTSD*) by transcription factor EB (TFEB), a master regulator of lysosomal biogenesis [158]. Finally, as discussed in the section "Homozygous Loss-of-Function Mutations in *GRN* Cause Neuronal Ceroid Lipofuscinosis", a complete loss of PGRN due to homozygous loss-of-function *GRN* mutations leads to NCL, a lysosomal storage disease characterized by the accumulation of autofluorescent storage material (lipofuscin) [52]. Interestingly, lipofuscin accumulation is also consistently seen in the brains of different $Grn^{-/-}$ mouse lines [130, 132, 134, 159, 160]. Accumulation of ubiquitin [72, 130, 132, 134–136] and p62-positive [132, 161, 162] protein aggregates and increased levels of lysosomal proteins such as CTSD and LAMP1/2 [162–164] have also been detected in $Grn^{-/-}$ mice.

But what evidence suggests that even a partial loss of PGRN, such as is the case in FTLD-*GRN* patients, is sufficient to develop lysosomal dysfunction or NCL-like pathology? First, sphingolipid activator protein (saposin) D and subunit c of mitochondrial ATP synthase (SCMAS), two major protein components of lipofuscin [165, 166], are elevated in patients with FTLD-*GRN* [163]. In addition, preclinical retinal lipofuscinosis was detected in retinas of heterozygous loss-of-function *GRN* mutation carriers, and increased lipofuscinosis and intracellular NCL-like storage material also occurred in circulating lymphoblasts as well as postmortem cortex of these patients. Interestingly, the NCL-like pathological changes found in lymphoblasts from heterozygous *GRN* mutation carriers could be fully rescued by normalizing PGRN expression [167]. Similarly, FTLD-*GRN* patient induced pluripotent stem cell (iPSC)-derived cortical neurons have been shown to develop NCL-like pathologies including enlarged vesicles and lipofuscin accumulation [168]. Together, these findings strongly suggest that PGRN plays vital roles in lysosomes and dysfunction of the lysosomes due

to (even a partial) loss of PGRN may be an important disease mechanism in FTLD-*GRN*. To provide further context to these recent developments, we will next summarize current insights into lysosomal trafficking of PGRN, its processing into granulins within lysosomes, and the functional evidence of the involvement of PGRN and granulins in the regulation of a growing list of lysosomal enzymes.

Lysosomal Trafficking of PGRN

Using an alkaline phosphatase-mediated cell surface binding assay, Hu et al. identified SORT1 as a high-affinity binding cell surface receptor for PGRN [89]. PGRN binds to the beta-propeller region of SORT1 in the extracellular domain through its last three amino acids (QLL) [89, 169]. SORT1 is a well-known sorting receptor [170]. The cytoplasmic tail of SORT1 encodes two sorting motifs, a tyrosine-based YSVL motif and an acidic dileucine cluster motif, which facilitate both endocytosis and intracellular trafficking of SORT1 [171]. Further studies found SORT1 functions as a sorting receptor for PGRN. It binds to PGRN both intracellularly and extracellularly and facilitates its lysosomal trafficking from the biosynthetic pathway and from the extracellular space [89] (Fig. 3). Overexpression of SORT1 reduces extracellular PGRN levels, whereas downregulation of SORT1 or abolishing the binding between PGRN and SORT1 increases extracellular PGRN levels [89, 169, 172, 173]. Interestingly, genetic knockout of *Sort1* in $Grn^{+/-}$ mice completely corrects PGRN serum levels from the haploinsufficiency state back to normal [89]. Notably, Carrasquillo et al. took a human genetic-based approach and performed a genome-wide association analysis of common genetic variants with human plasma PGRN levels. Genetic variants at the *SORT1* locus were found to be the most significantly associated with plasma PGRN levels, suggesting that differences in *SORT1* expression (predicted to result from these variants) also regulate extracellular levels of PGRN in vivo [173].

Importantly, while a complete loss of *Sort1* in mice leads to a robust accumulation of Pgrn in serum, a substantial amount of Pgrn (~50%) can still be detected in lysosomes in cortical neurons derived from these mice suggesting the existing of alternative lysosomal pathway(s) for PGRN, in addition to SORT1 [89]. Using an unbiased proteomic approach, Zhou et al. identified PSAP as a strong binding partner of PGRN [151]. Like PGRN, PSAP is also a secreted glycoprotein that is predominantly localized to lysosomes [174]. Similar to the binding to SORT1, PSAP binds to PGRN within the cell as well as in the extracellular space. Through further binding to two trafficking receptors (M6PR and LRP1), PSAP allows PGRN a piggyback ride and delivers it into lysosomes [151] (Fig. 3). Disruption of the binding of PGRN and PSAP completely abolishes the PSAP-mediated lysosomal trafficking of PGRN from both the biosynthetic pathway and extracellular space [175]. Loss of *Psap* in mice increases serum Pgrn level to a similar extent as loss of *Sort1* (~five- to sixfold) [89, 151]. Interestingly, Nicholson et al. independently demonstrated a physical interaction between PGRN and PSAP in functional follow-up experiments after genetic variants at the *PSAP* locus were found to be associated with human plasma PGRN levels [176].

Notably, PSAP-mediated lysosomal trafficking of PGRN is independent from the SORT1 pathway since loss of SORT1 failed to abolish PSAP-mediated lysosomal trafficking of PGRN. Moreover, the deficits of lysosomal trafficking of PGRN that resulted from the loss of PSAP can be fully rescued by overexpression of SORT1 [151]. Thus, the SORT1 and PSAP pathways are two complementary pathways that regulate the lysosomal trafficking of PGRN. The contribution that each of these two pathways plays in the lysosomal trafficking of PGRN might be determined by the expression levels or abundance of the pathway components in different types of tissues and different developmental stages. Indeed, SORT1 is almost undetectable in mouse fibroblasts, and as a consequence, the lysosomal trafficking is completely dependent

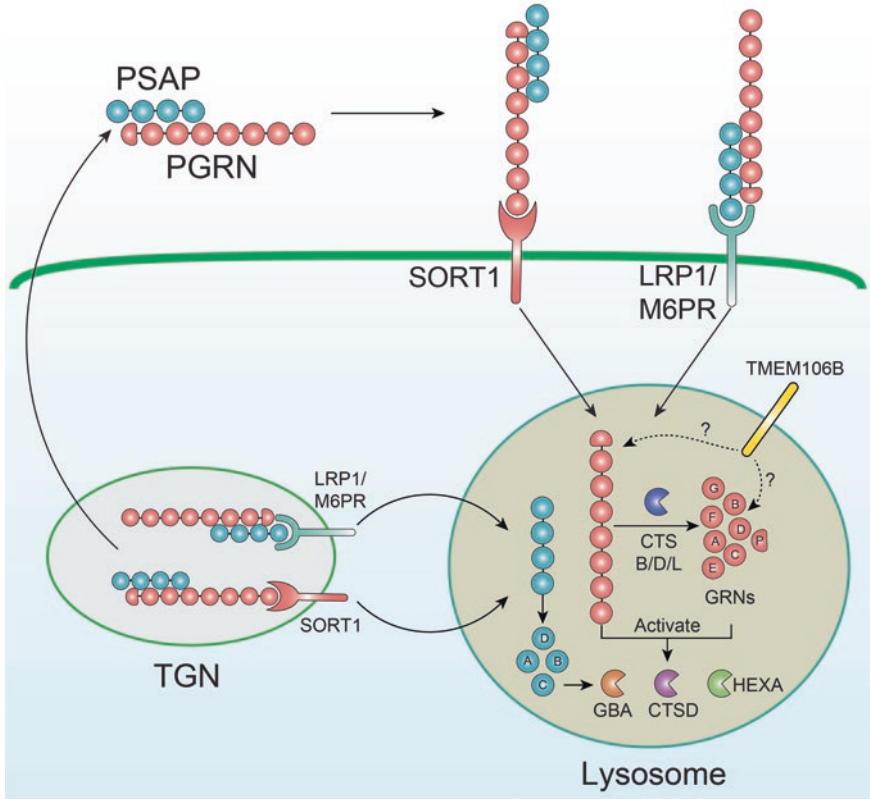

Fig. 3 Lysosomal trafficking and function of PGRN. Progranulin (PGRN) is targeted into lysosomes through either sortilin 1 (SORT1) or PSAP-LRP1/M6PR pathways from the extracellular space and trans-Golgi network (TGN). Lysosomal targeted PGRN is further processed into stable granulin peptides (GRNs) by lysosomal enzymes including cathepsin L (CTSL), cathepsin B (CTSB), and cathepsin D (CTSD). Recent work provided some first insights into the role of PGRN in lysosomes. It was suggested that PGRN may indirectly regulate lysosomal function by controlling the lysosomal trafficking and processing of prosaposin (PSAP) or may directly regulate lysosomal enzymes such as CTSD, glucocerebrosidase (GBA), and β-hexosaminidase A (HEXA) in concert with GRNs. TMEM106B might either directly or indirectly interact with PGRN and GRNs to co-regulate lysosomal function. *M6PR* mannose-6-phosphate receptor; *LRP1* low-density lipoprotein receptor-related protein 1

on PSAP, whereas in neurons where both SORT1 and PSAP/LRP1/M6PR are highly expressed, both pathways contribute to the lysosomal trafficking of PGRN. Taken together, these findings suggest SORT1 and PSAP pathways coordinate with each other to regulate the lysosomal trafficking of PGRN in a spatiotemporal-dependent manner. Further studies on examining lysosomal localization of PGRN in *Psap* and *Sort1* double-knockout mice will be important to reveal whether other pathway(s) might still exist.

Lysosomal Processing of PGRN

PGRN and PSAP share multiple biological features including lysosomal localization and trafficking mechanisms. In addition, PGRN and PSAP are both precursor proteins which can be further processed into a group of smaller mature functional proteins. Whereas PGRN had been shown to be proteolytically processed into seven and a half granulin peptides in the extracellular space [18], PSAP is proteolytically processed into four saposin peptides within lysosomes

[177]. Given these similarities, it was hypothesized that PGRN, like PSAP, could be processed into granulin peptides within lysosomes [178], which was eventually experimentally demonstrated by three independent groups in 2017 [120, 156, 157] (Fig. 3). Multiple lines of evidence were provided to support this important discovery: first, mature granulins were detected in multiple different cell lines including Hela, HEK293T, H4, SH-SY5Y, SW13, and primary fibroblasts as well as multiple different tissues such as brain, liver, spleen, kidney, and heart [120, 157]. Second, either disruption of the lysosomal trafficking of PGRN or inhibition of lysosomal activities abolished the generation of granulins suggesting that the intracellular processing of PGRN indeed occurs within lysosomes [120, 157]. Finally, in vitro cleavage assays directly showed multiple lysosomal proteases such as cathepsin L, B, and D are able to cleave PGRN into granulins [120, 156, 157]. The cleavage effects of these lysosomal proteases were further verified within cells by using different cathepsin knockout mouse fibroblasts [157]. Of note, in addition to stable granulins, multiple intermediate products, like di- or multi-granulin peptides, were also produced [120, 156, 157]. The observation of different cleavage patterns of PGRN upon incubation with different lysosomal proteases [157] suggested that the lysosomal processing of PGRN might require the coordination of different lysosomal proteases, further highlighting the complexity of PGRN processing and its regulation. Most important in the context of FTLD is the fact that haploinsufficiency of PGRN in $Grn^{+/-}$ mice and FTLD-*GRN* patients was shown to lead to a comparable reduction of the granulin peptides [120, 157]. Taken together, these findings clearly demonstrated that PGRN is converted into granulins within lysosomes. Further study toward the understanding of the function of individual granulins as well as its processing intermediates in lysosomes might ultimately reveal the disease mechanism of both NCL and FTLD caused by *GRN* mutation.

Lysosomal Function of PGRN

Effect on PSAP

In the section "Lysosomal Trafficking of PGRN", we described how PSAP binds to PGRN, thereby offering PGRN a way into lysosomes through PSAP receptors: LRP1 and M6PR [151]. Interestingly, the reverse also appears to take place. Specifically, PGRN can facilitate the lysosomal trafficking of PSAP through its receptor SORT1 [26]. Loss of *Grn* in mice compromised the neuronal lysosomal targeting of Psap leading to a reduction of neuronal lysosomal Psap and saposins and an increase of Psap in serum. Loss of *Sort1* also leads to a comparable increase of Psap in serum as compared to what is seen upon *Grn* loss. Similarly, neuronal PSAP and saposins were found to be decreased in FTLD-*GRN* but not control individuals or FTLD patients with tau pathology. Furthermore, it is known that loss of PSAP or saposins can also cause lysosomal storage disease [177]. Moreover, loss of *Psap* in mice results in FTLD-like behavioral phenotypes as well as FTLD-like pathologies including accumulation of phospho-TDP-43 (pTDP-43) and massive gliosis [26]. Together, these findings suggest that PGRN indirectly influences lysosomal function by controlling the lysosomal level of PSAP and saposins and that reduced levels of neuronal lysosomal PSAP and saposins due to the haploinsufficiency of PGRN may be a contributing factor in the development or progression of FTLD-*GRN*.

Effect on CTSD

Recently, multiple groups independently demonstrated a surprising role of PGRN and granulins in the regulation of cathepsin D (CTSD) enzymatic activity [167, 168, 180, 181]. CTSD is an important aspartyl protease responsible for the degradation of proteins in lysosomes. PGRN directly interacts with CTSD [168, 180, 181] and increases its enzymatic activity [168, 180]. Furthermore, granulin E is also able to bind CTSD [181], and co-incubation of granulin E with CTSD is sufficient to stimulate the proteo-

lytic activity of CTSD in vitro [168, 180]. In support of the function of PGRN in CTSD activity regulation, loss of *Grn* in different mouse tissues such as brain, liver, and spleen [180, 181] as well as the partial loss of PGRN in human fibroblasts [167] and iPSC-derived human cortical neurons from FTLD-*GRN* patients [168] resulted in a reduction of CTSD activity. In fact, elevated CTSD protein level was detected in both postmortem brains of FTLD-*GRN* patients [163] and *Grn*-deficient mouse tissues [163, 180], likely due to a feedback loop resulting from the reduced CTSD activity. Most recently, in vitro experiments found PGRN may enhance the conversion of the CTSD precursor to mature CTSD in a concentration-dependent manner [182]. Combined with the fact that loss of *Ctsd* in mice was shown to induce pTDP-43 aggregates [163], these findings suggest that reduced CTSD activity due to PGRN haploinsufficiency might play a role in the development of FTLD-*GRN*.

Effect on GBA

An important association of PGRN with glucocerebrosidase (GBA), a lysosomal enzyme involved in the glucocerebroside degradation, has also been revealed [183–187]. Homozygous *GBA* mutations cause Gaucher disease (GD), a common lysosomal storage disease [188], whereas heterozygous *GBA* mutations are associated with Parkinson's disease and Lewy-body dementia [189]. Jian et al. recently reported an association of decreased serum PGRN levels with GD [183]. In the animal study, they showed that under challenging conditions such as ovalbumin-induced chronic inflammation or during aging, $Grn^{-/-}$ mice develop GD-like phenotypes, including typical Gaucher-like cells in lung, spleen, and bone marrow as well as GD-like lysosomal morphological changes [183]. Mechanistically, they speculated that loss of PGRN leads to disruption of lysosomal trafficking of GBA, but the enzymatic activity of GBA was not affected [183, 184]. Inconsistently, loss of *Grn* in mice has been shown to result in a significant reduction of GBA activity in multiple different tissues including liver, spleen, and brain [185]. The reduced GBA enzymatic activity has been further confirmed in postmortem brains from FTLD-*GRN* patients [187]. Importantly, comparable amounts of GBA were detected in the lysosomal fractions of wild-type and $Grn^{-/-}$ mouse tissues strongly arguing that this *Grn* deficiency-mediated reduction in GBA activity is unlikely due to its lysosomal trafficking deficits [185]. Notably, although PGRN and granulins bind to GBA, addition of recombinant PGRN or granulins fails to increase GBA activity in vitro suggesting the contribution of indirect mechanisms. In this regard, it is known that saposins, the processing products from PSAP, positively regulate GBA activity [190]. CTSD is the major protease for PSAP processing [191], and its activity is further regulated by PGRN as described above [167, 168, 180, 181]. Thus, it is possible that PGRN regulates GBA activity through its control on the CTSD-PSAP-saposin axis. Indeed, a recent study showed loss of PGRN impairs the processing of PSAP to saposin C and the treatment of saposin C rescued the reduction of GBA activity in PGRN-deficient cells [186].

Effect on HexA

Most recently, PGRN has been associated with β-hexosaminidase A (HexA) [192], a lysosomal enzyme that is involved in GM2 ganglioside degradation. Loss of Hex A results in GM2 ganglioside accumulation, leading to Tay-Sachs disease (TSD), a typical lysosomal storage disease [193]. PGRN binds to HexA and increases the enzymatic activity and lysosomal delivery of HexA. Both aged and ovalbumin-challenged adult *Grn*-deficient mice were shown to have significant GM2 ganglioside accumulation and the appearance of typical TSD cells containing zebra bodies [192]. Treatment of either recombinant PGRN or Pcgin, an engineered PGRN derivative, reversed PGRN deficiency-induced lysosomal accumulation of GM2 ganglioside.

Lessons from TMEM106B

Genetic studies have clearly established *TMEM106B* variants as genetic modifiers of disease risk in *GRN* mutation carriers [37, 194, 195]. While the functional variant(s) responsible for the risk-modifying effect remain largely

unknown, multiple studies have suggested that the "risk" haplotype is associated with higher levels of transmembrane protein 106B (TMEM106B) as compared to the "protective" haplotype [194, 196]. Mechanistically, it has been suggested that a noncoding variant could change the transcription of *TMEM106B* by altering chromatin architecture [196]; however, a role of the coding p.T185S variant cannot be excluded [197–199].

Given that TMEM106B is a type II transmembrane protein with its main intracellular localization at lysosomes [198, 200, 201], this genetic finding provides independent support for the important role of PGRN in lysosomes and its possible dysfunction in FTLD-*GRN*. Overexpression of TMEM106B in vitro results in multiple lysosomal dysfunctions, including enlarged lysosomal size, reduced lysosomal pH, decreased degradation capacity of endocytic cargo, and deficits of endolysosomal trafficking [198–202], eventually leading to cell death [203]. Elevated levels of TMEM106B have been found in postmortem brains of FTLD-TDP patients [200, 204] as well as brains of $Grn^{-/-}$ mice [160]. Furthermore, increased TMEM106B exacerbated

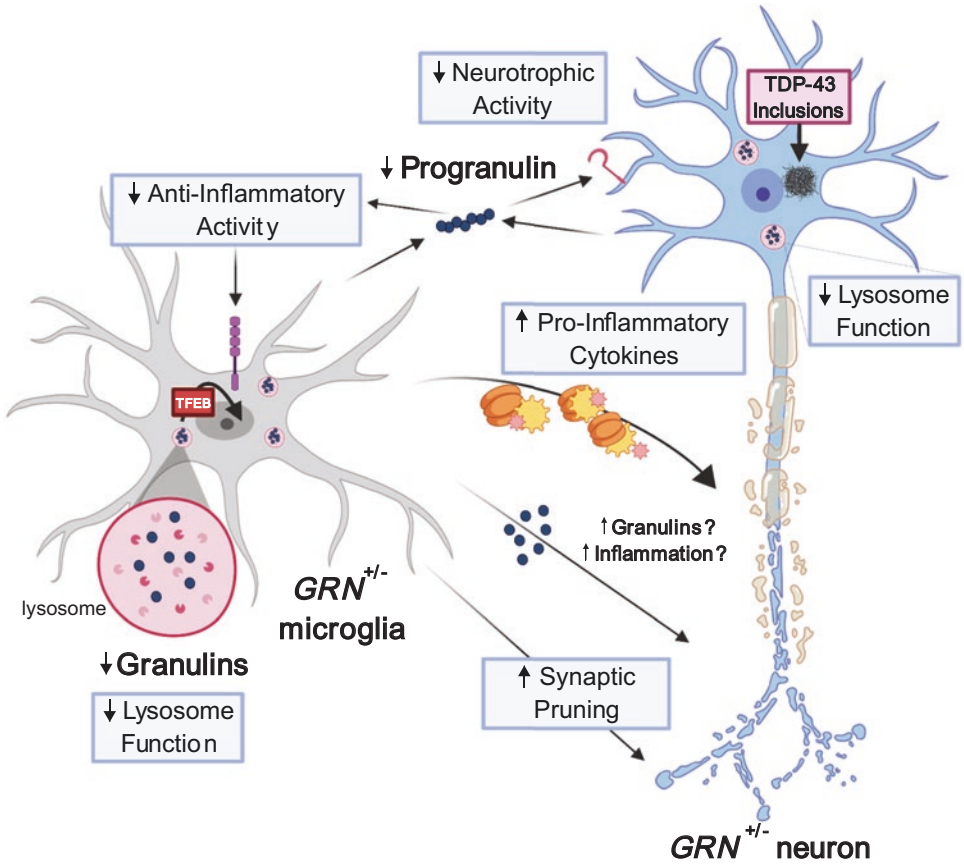

Fig. 4 Summary of potential disease mechanisms in FTLD-*GRN*. Progranulin (PGRN) is secreted by neurons and microglia in the brain, which can have beneficial activity through neurotrophic support and/or suppressing inflammation, both of which are decreased by PGRN haploinsufficiency. PGRN is normally trafficked to the lysosome in neurons and microglia, processed into granulins, which are thought to have a homeostatic function. The extracellular role of granulins in the brain is unclear but may increase inflammation. In neurons, decreased lysosomal function leads to defects in protein homeostasis and accumulation of ubiquitinated TDP-43 inclusions. In microglia, lysosome dysfunction can activate TFEB, which may exacerbate the release of pro-inflammatory cytokines and increase synaptic pruning, contributing to neuronal toxicity and degeneration

the FTLD-related pathologies such as lipofuscin and lysosome dysfunction in *Grn−/−* brains at old age [160]. Intriguingly, loss of Tmem106b in $Grn^{-/-}$ mice was shown to ameliorate both the lysosomal and FTLD-related phenotypes in young $Grn^{-/-}$ mice [205]. Other studies, however, failed to observe noticeable benefits from the loss of Tmem106b in heterozygous $Grn^{+/-}$ mice and in C9orf72-repeat overexpressing mice, a mouse model for another type of FTD-TDP, where genetic studies had also identified a disease-modifying effect for *TMEM106B* haplotypes [206, 207]. Moreover, our unpublished work shows loss of *Tmem106b* results in myelination deficits and further loss of *Tmem106b* in $Grn^{-/-}$ mice exacerbates its FTLD-related pathologies leading to severe motor deficits (*personal communication*). These studies underscore a functional interaction between TMEM106B and PGRN, but additional mechanistic insight into the biology of either one of these proteins remains to be learned. They also illustrate that more work is needed before lowering TMEM106B can be considered as a therapeutic strategy in *GRN* carriers.

Concluding Remarks

Almost 14 years after the initial discovery of *GRN* mutations in FTLD patients, important new insights into its function and dysfunction have emerged. At least three independent disease mechanisms have been proposed to contribute to the development of FTLD-*GRN*: a loss of neurotrophic support, an increase in neuroinflammation, and lysosomal dysfunction (Fig. 4). In individual patients, a combination of these pathways may well be involved, potentially modified by additional genetic and/or environmental factors. In parallel to this increase in knowledge, global efforts have emerged to prepare the field for PGRN-related clinical trials by focusing on the identification of cohorts of mutation carriers and the development of robust biomarkers of disease onset and progression [208, 209]. It is the hope that the significant progress in this field will lay the foundation for the future development of successful therapies for FTLD-*GRN*. However, until then, key outstanding questions remain to be answered in relation to the normal function of PGRN and its role in disease, including but not limited to: (1) What is the lysosomal function of PGRN and/or granulins? (2) Which receptors are most critical for the neurotrophic and inflammatory activities of PGRN and granulins? (3) How does the PGRN-granulin balance affect disease development or progression? (4) What is the functional interaction between PGRN and granulins and TMEM106B within lysosomes? Future studies should focus on these important topics.

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Trends in Understanding the Pathological Roles of TDP-43 and FUS Proteins

Emanuele Buratti

Abbreviations

ALS	Amyotrophic lateral sclerosis
FTLD	Frontotemporal lobar dementia
FUS/TLS	Fused in sarcoma/translocated in liposarcoma
hnRNP	Heterogeneous ribonucleoproteins
lncRNA	Long noncoding RNA
mRNA	Messenger RNA
miRNA	MicroRNA
TDP-43	TAR DNA binding protein 43 kDa

Introduction

The involvement of TAR DNA binding protein-43 (TDP-43) in neurodegenerative diseases was first described in 2006 when this protein was shown to be the main component of the characteristic aggregates found in the brains in patients with amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) [1, 2]. This discovery was swiftly followed 3 years later by the identification of fused in sarcoma (FUS) as another TDP-43-related protein that was aggregating in the neurons of a subset of familial ALS and sporadic FTLD cases [3, 4]. Since then, the number of RNA binding proteins (RBPs) that have been shown to be involved in ALS/FTLD has increased considerably. It now includes several other RNA binding proteins such as EWS (Ewing sarcoma breakpoint 1, also called EWSR1) and TAF15 (TATA box binding protein-associated factor 68 kDa) [5], heterogeneous ribonucleoproteins (hnRNP A1 and hnRNP A2/B1) [6], Matrin-3 (MATR3) [7], ataxin-2 (ATXN2) [8], and T-cell intracellular antigen 1 (TIA1) [9–11]. More recently, the identification of DNA and as a consequence RNA repeat expansions in the C9orf72 gene [12, 13] has allowed to greatly expand the crucial role of RNA alterations in the ALS/FTLD phenotype and has extended the number of RNA-mediated pathways that can lead to disease [14–18].

Taken together, all these findings have firmly established RNA metabolism as a major contributor of ALS/FTLD processes in humans [19–23], and the emerging picture is that a combination of RNA processing alterations might represent the principal contributor to the occurrence of both ALS and FTLD in patients [17, 24, 25]. This conclusion does not really simplify matters in terms of knowing exactly why neurons die because RNA processing basically regulates all the processes within a eukaryotic cell. Therefore, the number of pathways that could eventually become disrupted following TDP-43 and FUS aggregation is steadily growing and ranges from such diverse extremes as DNA plasticity and

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damage [26], pre-mRNA splicing [27], nucleocytoplasmic transport [28, 29], polyadenylation [30], or RNA translation [31–34]. Once impaired, these basic mechanisms can then induce misregulation of more complex processes such as endocytosis [35], neuroinflammation [36, 37], autoimmunity [38], mitochondrial functions [39], stress granule formation [40–43], epigenetics mechanisms [44], and even alterations at the general metabolic profiles of patients [45, 46]. Therefore, the aim of this chapter will be to highlight promising future trends in TDP-43/FUS research that will hopefully lead to the identification of pathways that play an important role in disease and, most importantly, that can be considered "druggable" with the technical means at our disposal.

TDP-43 and FUS Protein Structure

TDP-43 protein structure, mutations, and its posttranslational modifications have recently been described in several recent reviews [47–50] (Fig. 1). For this reason, just a brief summary will be presented in this chapter. Basically, at the structural level, TDP-43 possesses a well-structured N-terminus region [51, 52] that carries a nuclear localization signal [53] and is involved in protein dimerization/oligomerization [51, 54]. This is important for TDP-43 splicing functions [55] that are mainly regulated by two RRM (RNA recognition motif) domains that closely follow the N-terminus of the protein. These domains are required to bind target RNA mostly in a sequence-specific manner [56, 57] but are also participating in the aggregation process of this protein through being prone to self-assembly [58]. Finally, the sequence of TDP-43 is completed by a mostly unstructured C-terminus region that has prion-like properties (PrLD), is mainly used to interact with other proteins, and plays a fundamental role in phase separation and aggregation of this protein [59].

Similar to TDP-43, FUS is an hnRNP protein originally found translocated in human liposarcomas and for this reason was also denoted as TLS [60, 61]. Originally, FUS was also called hnRNP P2 [62], and it belongs to the FET protein family that includes two other RBPs, EWS and TAF15, that have also been found to be involved in FTLD [63, 64]. The FUS structure consists of several domains that have been reviewed in detail elsewhere [65] (Fig. 1), and it consists of an N-terminal

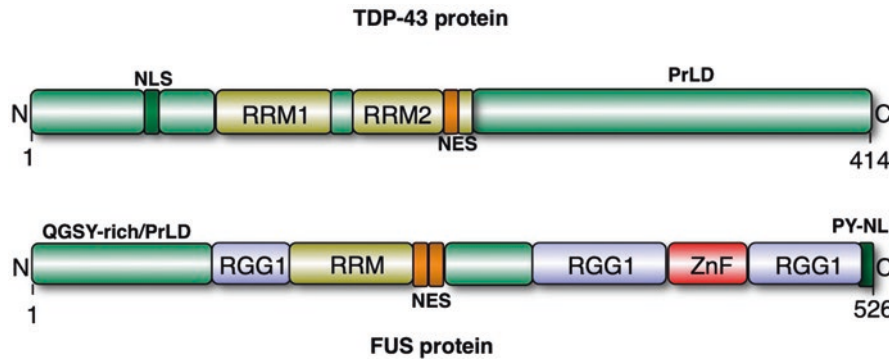

Fig. 1 This figure shows a schematic domain structure of TDP-43 and FUS. TDP-43 is a 414-long protein characterized by two RNA recognition motifs (RRM), RRM1 and RRM2 (which contains a putative nuclear export sequence, NES) that are the main regulators of RNA binding. At the N-terminus, there is a highly structured region that regulates oligomerization of this protein and contains a nuclear localization signal (NLS), while at the C-terminus there is a mostly unstructured region that is responsible for protein-protein interactions and has characteristics of a prion-like domain. On the other hand, the 526-residue-long FUS protein contains a single RRM domain, and its unstructured, prion-like region is localized at the N-terminus of the protein. FUS further contains two adjacent putative NES sequences, three arginine-glycine-glycine-rich domains (RGG1-3), and a zinc-finger motif (ZnF) that contribute to stabilize RNA binding. The nuclear localization signal of FUS is located at the very C-terminal of this protein (PY-NLS)

domain with a QGSY-rich region, also described as a prion-like domain (PrLD) that is responsible for FUS dimerization and binding to chromatin for regulation of transcription initiation [66]. This region is followed by a highly conserved RRM domain whose structure has been solved in solution alone [67] or bound to RNA [68]. In general, the presence of unstructured prion-like domains and the RNA binding ability are probably the major unifying factors of TDP-43 and FUS. However, they do not bind in exactly the same positions because the FUS consensus binding sequence could never be as clearly defined as it was for TDP-43. In particular, CLIP analyses have shown that FUS binds preferentially in a sawtooth manner within long introns in neuronal cells [69], while TDP-43 prefers UG-rich and a few other selected motifs [70–72].

Interestingly, and similarly to TDP-43, the FUS RRM has also been shown to be prone to self-assembly to form amyloid fibrils [73] although for the FUS RRM domain, there does not seem to be a linear consensus motif [74]. This RRM region is then followed by a zinc finger motif and multiple RGG repeats that are located at the C-terminal end and can also participate in RNA binding [68]. All these domains act together to mediate both protein-RNA and protein-protein interactions in the multiple activities of this protein.

Disease-Associated Mutations in TDP-43 and FUS

In the early days of TDP-43 and FUS research, and in the absence of robust functional studies (which later became available), the presence of TDP-43 aggregates in patients did not represent by itself a sufficient condition to establish TDP-43 as a disease-causing gene [75]. In this early context, therefore, the first direct link of TDP-43 with disease was provided by the discovery of mutations within its encoding gene *TARDBP*, which were shown to segregate with disease among family members [76–78]. To this date, more than 50 missense mutations together with few truncation and insertions/deletions have been reported in the literature. These mutations account for about 5% of familial ALS cases and have also been found in a few FTLD cases [49]. The functional significance of these mutations is for the most part still unknown, although several have been described to affect the liquid-liquid separation properties of TDP-43 [79], RNA binding [80], or posttranslational modifications such as phosphorylation [81] and acetylation [82, 83]. In general, mutations are likely to be associated with features that can be directly connected with basic TDP-43 properties within cells, such as altered subcellular localization, protein half-life, or protein-protein interactions [49]. In some cases, mutations have been shown to affect directly important neuronal functions. For example, a disease-associated mutation of TDP-43 (A315T) has been recently described to affect dendritic spine assembly in an ALS mouse model [84], and other mutations have been shown to impair RNA axonal transport [85].

Similarly to TDP-43, mutations in FUS can be found in about 4% of familial ALS cases and less than 1% of sporadic ALS cases [65, 86]. Unlike TDP-43, however, these mutations can be found in almost all regions of the protein, although the most severe ones in terms of early occurrence of the pathology primarily affect the C-terminal domain where the nuclear localization sequence resides [3, 4]. A detailed overview of *FUS/TLS* mutations can be found in recent review articles [87]. Most importantly, mutations altering the cytoplasmic mislocalization of FUS/TLS can compromise the autoregulation process of this protein and promote its increase and abnormal accumulation in the cytoplasm [88]. At a more general level, FUS mutations have also been associated with a drastic reduction in nuclear GEM structures and decreased binding to the essential U1-snRNP splicing factor, causing a general impairment of the splicing process [89–92]. Regarding this issue, mutant FUS proteins have been shown to change their binding affinity consistently as a consequence of their abnormal localization and redistribution in the cytoplasm [93]. Alternatively, some FUS mutations have also been shown to act in a similar manner to TDP-43 mutations, for example, in their ability to

sequester paraspeckle components in the cytoplasm [94, 95] or to affect the interaction with other RNA binding proteins, such as ELAVL4, that will eventually be included in the cytoplasmic inclusions [96].

In conclusion, although mutations in TDP-43 and FUS are quite rare in ALS/FTLD patients, they certainly seem to play a role in the pathology and could theoretically be used as a target in therapeutic intervention [97]. Most importantly, however, their study has also helped to uncover novel molecular aspects of the disease such as DNA damage [98, 99] or the importance of autoregulatory processes, as recently observed in a mouse expressing the TDP-43 disease-associated mutant Q331K [100].

Therefore, the functional study of TDP-43 and FUS mutations plays a very important role in our better understanding of the disease. Interestingly, it should be noted that this usefulness is not unique with regard to natural mutations but is true also for artificial mutations obtained through ENU mutagenesis. For example, a gain-of-function artificial mutation in TDP-43 (M323K) has recently allowed to reveal a novel category of splicing events controlled by TDP-43 that consists in the skipping of constitutive exons from several cellular genes that play an important role in proteostasis, and this loss was associated with adult-onset motor neuron loss and neurodegenerative changes in a mouse model of ALS [101].

Major Pathological Features of ALS/FTLD Associated with TDP-43 and FUS

Although the study of disease-associated mutations is important to better understand several aspects of disease, it is now also clear that TDP-43 and FUS mutations are very rare in patients. Therefore, they may not necessarily recapitulate the most common pathological features of TDP-43 and FUS aggregation in neurons. In most patients, in fact, the most common pathological feature shown by these proteins is represented by the aberrant aggregation of the wild-type proteins in the body of affected neurons.

In ALS, almost all cases present TDP-43 inclusions with the exception of patients with mutations in FUS or SOD1 [102, 103]. On the other hand, in FTLD, TDP-43 inclusions are present in almost half of the cases (45%), and wild-type FUS has been shown to abnormally aggregate in a subset of FTLD cases (9%) with the rest characterized by Tau pathology [104]. For reasons that are still not clear, TDP-43 and FUS proteins do not seem to co-localize in the same pathological aggregates, although wild-type TDP-43 has been observed to bind with low affinity to FUS [105], and in yeast models both proteins have been reported to co-aggregate very efficiently [106].

A second important feature of the pathology is that these proteins are variably modified at the posttranslational level. In fact, within the pathological aggregates, TDP-43 is aberrantly ubiquitinated, phosphorylated, acetylated, sumoylated, and cleaved to generate C-terminal fragments [1, 2, 82, 107, 108]. Interestingly, aberrant phosphorylation of TDP-43 has also been observed in other diseases such as inclusion body myopathy [109] or Niemann-Pick C [110]. Compared to TDP-43, FUS is methylated in its C-terminal arginine residues, and this modification seems to be specifically associated with the formation of cytoplasmic FUS inclusions in FTLD-FUS patients [111]. More recently, FUS phosphorylation has been described to occur in its low complexity domain, and this can affect its ability to phase separate and aggregation propensity [112]. How and to what extent these posttranslational modifications may contribute to the formation of pathological TDP-43 aggregates in patients still remains an open issue that deserves further investigation [48].

An important issue that is also still open regards their potential amyloid composition of the TDP-43 and FUS aggregates. Initially, aggregates that were described in patients did not seem to possess an amyloid nature [1, 2], and TDP-43 inclusion bodies are of an amorphous nature [113]; under certain conditions, TDP-43 and FUS have also been observed to adopt amyloid conformations [114, 115]. In particular, selected fragments of the TDP-43 C-terminus have a very

high propensity to form amyloid-like fibrils in vitro [116–122]. Similar to TDP-43, FUS inclusions in patients could not be stained by amyloid-detecting dyes such as Congo red and thioflavin B [123]. However, a segment with a strong amyloid-forming tendency that could induce the seeded aggregation of FUS has been recently isolated [124], and FUS RRM domains have been reported to undergo irreversible unfolding to self-assemble in amyloid fibrils [73]. Taken together, all these evidences point toward a condition where, although late-stage TDP-43 and FUS aggregates do not display typical features of amyloid aggregates, a few of the steps that lead to their aggregation may include amyloid formation and could thus be inhibited by drugs that are designed against this process.

From a therapeutic point of view, however, a priority target is to better understand the mechanisms that lead to protein aggregation, and several factors have been described which promote this event, especially for TDP-43 [125]. Regarding this issue, it should be noted that TDP-43 and FUS are aggregation-prone proteins that have a tendency to aggregate even following small increases in their endogenous expression levels [125, 126]. As a result, many different types of stimuli can trigger their aggregation and include already described mutations or lower efficiency of the autophagic/proteasome pathways (discussed below).

In physiological conditions, one of the connections that can probably play an important but not exclusive role [127] in the pathological aggregation of these proteins is represented by their recruitment in stress granules (SG) [40, 128, 129]. It is now well accepted that both TDP-43 and FUS are recruited to SGs in condition of different environmental insults [130, 131], and several reports have strengthened their connection with ALS/FTLD disease [132, 133]. In stressful conditions, the purpose of SGs is to arrest translation of housekeeping proteins by transiently sequestering cellular mRNAs. In this way, SGs promote the selective translation of stress-response proteins to help cellular recovery. Following stress removal, SGs normally dissolve quickly, and mRNA translation goes back to normal. However, using advanced optogenetic techniques, it has been shown that following the persistence of a stressful condition within cells, the SGs eventually evolve to form aberrant aggregates that could then lead to the pathological cascade [43]. At present, there are no therapeutic strategies that target specifically stress granules in disease. Importantly, recent evidence has shown that a class of small planar molecules can reduce the association of SGs with TDP-43 in iPSC-derived patient motor neurons and prevent accumulation of this protein in the cytoplasm [134]. Of course, although promising, the therapeutic potential of all these approaches will have to be tested in more complex animal models.

Categorizing TDP-43 and FUS Pathological Functions Within Cells

Since their identification, many studies have targeted the issue of clarifying the pathological role of aggregates once they have sequestered the soluble pool of TDP-43 and FUS in the nuclear and cytoplasmic compartments. Although a lot of progress has taken place in this area, it is far from being understood [135]. In general, protein aggregates within neurons can be directly toxic or they can become so, by acting as "protein sinks," thus depleting the cell of active proteins. Alternatively, aggregates may also be considered protective when they serve to remove mutated proteins that might be toxic when produced in excess or whose degradation becomes impaired. Finally, a third possibility is that aggregates may represent mere epiphenomena of the disease and not directly connected with the pathology.

With regard to TDP-43, some lines of evidence support the possibility that the aggregates may have a direct toxic role [113, 136, 137] as they may interfere with the nucleocytoplasmic transport of both proteins and RNA in the cell [138] or an indirect toxic role that could be induced by the sequestration in the aggregates of other proteins with which TDP-43 and FUS are normally in close contact within the cellular environment [64, 139–141]. However, there is also evidence that aggregates may be protective, at

least during the early stages of the disease. This hypothesis has been supported by studies in TDP-43 *Drosophila* models [142] and somewhat reminds a situation that has been observed for Huntington's disease [143]. More recently, random mutagenesis of the TDP-43 prion-like domain to express more than 50.000 mutants has shown that mutations that increase hydrophobicity and aggregation can decrease toxicity [144]. Nonetheless, a consensus is still lacking, and readers are referred to several reviews dealing with this specific issue [145–149].

In keeping with these views, it is very likely that a combination of both gain- and loss-of-function effects, not necessarily linked in a temporal manner, may result in the alteration of the many nuclear and cytoplasmic functions of these proteins within neurons [107, 150–152] (Fig. 2) that will be described in the next section. As can be expected, the very high evolutionary conservation of both TDP-43 and FUS means that their alteration in the nucleus and cytoplasm will result in harmful consequences with regard to many cellular processes and pathways, and they could be most pronounced in neurons given their extremely complex architecture and metabolism.

Altered Cellular Pathways Mediated by TDP-43 and FUS Within Cells

As already mentioned, following aberrant aggregation and concurrent nuclear depletion of TDP-43 and FUS, there are several nuclear and cytoplasmic pathways that are likely to become disrupted (Fig. 2). The following list aims to briefly describe all the major ones that have been identified so far:

- *Response to DNA damage*. Maintaining the integrity of DNA in postmitotic neurons that do not divide during the entire life of an individual is a particularly critical issue with regard to their survival. At the proteomic level, both TDP-43 and FUS have been described to bind several factors important for DNA repair mechanisms [153]. In the case of TDP-43, a growing body of evidence has shown that alterations in TDP-43 expression may affect this process. For example, it has been demonstrated that this protein can induce neurodegeneration by compromising the functionality of chromatin remodeler Chd1/CHD2 that prevents appropriate expression of protective genes [154]. Moreover, overexpression of TDP-43 in *Drosophila* has been shown to induce cell death due to many alterations, including DNA damage [155]. At the moment, experimental evidence has suggested that TDP-43 may recruit the XRCC4/DNA ligase 4 complex at sites of double-strand breaks and thus act as a key component of the nonhomologous end joining (NHEJ) pathway that represents the major repair pathway in postmitotic neurons [156, 157].
- On the other hand, much more is known about the connection between FUS and DNA repair: the first evidence that FUS is involved in DNA repair came from its ability to promote D-loop formation and homologous recombination during DNA double-strand break repair [158]. In keeping with this finding, embryonic fibroblasts and B-cells from *k*nockout mice show genomic instability and chromosome breaks [159]. Following DNA damage, FUS is phosphorylated in its N-terminal serine residues by ATM and DNA-PK [160] and directly interacts with PAR polymerase and HDAC1 protein at the site of DNA damage [161–163]. Furthermore, in conditions of DNA damage, the FUS proteins increase its binding affinity toward the two histone acetyltransferases CBP and p300, thereby repressing their transcriptional activities [164].
- Although rather premature at the moment, all these indications suggest that DNA repair-targeted therapeutic avenues might become a promising avenue in the fight against ALS and FTLD.
- *Transcription.* The TDP-43 protein was originally described to repress HIV-1 virus replication when integrated in the human genome [165]. Although this property could not be confirmed in later studies [166], there are now a few genes where TDP-43 has been described to act as an "insulator," for example, in the

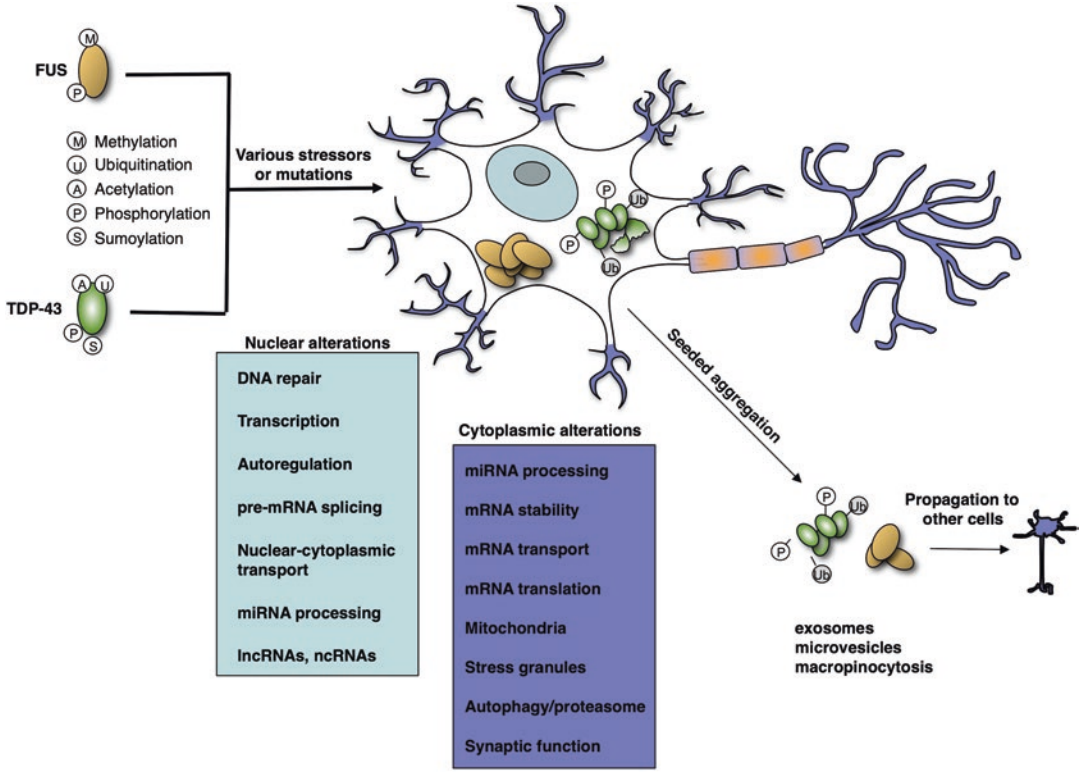

Fig. 2 This figure shows a schematic diagram of TDP-43 and FUS regulated cellular functions that can be affected following their aggregation in neurons. At the basic molecular level, the aggregation of these proteins causes a widespread dysfunction in many processes that occur both in the nucleus and the cytoplasm, from DNA damage repair mechanisms to mRNA translation. The dysfunction of these processes will then induce defects in many organelles (e.g., mitochondria) or complex cellular processes (such as stress granule dynamics, autophagy, and lysosomal processes). The presence of these defects, even if not immediately fatal to the neuron, will eventually induce its premature death with the possible spreading of aggregates or toxic oligomers to nearby cells through extracellular traveling mediated by vesicles (EVs) or other mechanisms

case of the *SP-10* gene in mice [167]. More conventionally, TDP-43 has also been identified as a transcriptional promoter in the case of the *TNF-alpha* gene [168] or as a transcriptional repressor of the VPS4B gene [169]. At the moment, however, it is not very clear what could be the importance of these alterations in disease and what is the molecular mechanism that mediates these effects.

– Contrary to TDP-43, the association of FUS with transcription has been much better defined. Indeed, FUS was originally identified in association with the genomic translocation of its N-terminal domain to fusion genes in a variety of liposarcomas and in myeloid leukemia to alter the transcription of the resulting chimeric genes [60, 61]. In addition to these specific events, FUS has also been shown to directly regulate the activity of RNA-pol II by controlling its phosphorylation during transcription [170], and disease-associated mutations have been shown to decrease its binding to RNA-pol II [171] and to active chromatin [66], leading to a reduced regulation of general transcription rates. Finally, the ability of FUS to bind near to alternative polyadenylation sequences has been associated with regulation also of this process [172]. At present, however, no specific therapies have been hypothesized that specifically target this characteristic feature of the FUS protein.
– *Autoregulation of their own expression*. Many RNA binding proteins regulate their own expression in cells by targeting their own pre-

mRNA and inducing changes in their processing to allow proper translation or induce degradation [173]. An important pre-mRNA target of TDP-43 is its own transcript that has been shown to undergo a splicing event in its 3'UTR region to regulate the differential use of *TARDBP* alternative polyadenylation sites [174]. Although still to be exactly defined, this mechanism allows the autoregulation of protein expression within cells in order to keep TDP-43 protein levels within a physiological range [174]. At present, there are indications that perturbations in this system, either due to mutations in TDP-43 or through artificial inhibition of the splicing event in the 3'UTR of TDP-43 that regulates its recognition, could be linked to the pathological phenotype [100, 175].

- In a manner similar to TDP-43, FUS can autoregulate its expression by binding to its own pre-mRNA [88]. The autoregulation mechanism is controlled by a process called nonsense-mediated decay [176]. This autoregulation can also be mediated by specific miRNAs that bind to FUS 3'UTR sequence and whose expression is affected by FUS itself [177].
- From the point of view of the pathology, it is easy to understand how aggregation of both TDP-43 and FUS may lead to a dysfunction in autoregulation. In particular, sequestration of TDP-43 or FUS in the aggregates will result in starting a vicious cycle where lack of these proteins would result in increased expression that would then lead to even more aggregation, and this will eventually result in increasingly harmful gain- or loss-of-function effects on the RNA metabolism [178]. In summary, it is very likely that future therapeutic strategies will be aimed at modulating this specific mechanism (although it might prove difficult to avoid an excessive stimulation or degradation of TDP-43 and FUS mRNAs).
- *Pre-mRNA splicing processes*. TDP-43 initial involvement in the regulation of pre-mRNA splicing was first identified for exon 9 in the *CFTR* gene [179]. Recently, several high-throughput studies have addressed in detail all the splicing alterations that occur in human ALS/FTLD patients or TDP-43 mice disease models [71, 180–182]. However, many of these events are probably not direct targets of TDP-43 and originate from changes in other splicing factors controlled by TDP-43 [183]. Nonetheless, several direct targets of TDP-43 have been identified in recent studies, and they include *POLDIP3/SKAR* [34, 184], *SORT1* [185, 186], *STAG2, MADD* [187], and *TNIK* [188] pre-mRNAs. In addition, among these targets, there are also important proteins for neurodegeneration that include hnRNP A1 [189], Tau [190], and SMN [191]. In addition, transcriptomic analyses from ALS-FTD patients and animal models of disease have shown that TDP-43 has the very important function of repressing the inclusion of cryptic exons [101, 192, 193]. These exons are normally excluded from the mature mRNA and, when inserted, will often cause a change in the reading frame and thus the introduction of premature translational stop codons. At present, their contribution to disease has not been clearly established, although TDP-43 splicing repression seems to be a key general feature for maintaining motor neurons in good health [194]. Nonetheless, once identified, splicing events that might play a critical role in ALS pathology would represent ideal therapeutic targets considering that their inclusion is strongly repressed in normal conditions.
- Like TDP-43, FUS involvement in splicing has been well studied. At the general level, the link between FUS and splicing is supported by reports describing its binding to the SMN protein, U1 small nuclear ribonucleoprotein (snRNP), and Sm-snRNP complex [89, 195]. In particular, FUS has been shown to bind to nascent pre-mRNAs and acts as a molecular mediator between RNA-pol II and U1-snRNP [196]. At the RNA level, FUS can also control histone transcript 3' end processing during the S replication phase of the cell cycle by interacting with the U7 snRNP complex and the transcriptional apparatus [197]. As with TDP-43, several studies have tried to define the splicing targets of FUS/TLS by high-

throughput assays in several disease models [69, 93, 188, 198–202]. However, like with TDP-43, these comparisons have resulted in little overlap among all published datasets [203], and more efforts will be required to determine exactly what are the splicing targets of FUS depending on individual cellular contexts. Finally, an interesting difference between TDP-43 and FUS is the observation that FUS can also affect minor intron splicing by interacting specifically with the key minor intron component U11snRNP and trapping it in the aggregates [204].

– *miRNA processing*. The dysregulation of miRNA expression following TDP-43 and FUS aggregation may have potentially very harmful consequences on neuronal cell survival in ALS [205] and other common diseases such as Alzheimer's, Parkinson's, and Huntington's [206]. Even before TDP-43 and FUS were found to be involved in neurodegenerative diseases, it was described that these proteins are present in the Drosha complex [207] and that TDP-43 is associated with perichromatin fibrils [208] that correspond to the region where miRNA processing occurs. Indeed, during neuronal differentiation, TDP-43 has also been shown to control Drosha protein stability, thus potentially affecting the biogenesis of the entire cellular miRNA population [209]. Finally, in human neuronal cell lines, TDP-43 depletion has also been associated with a consistent increase of DICER mRNA and protein levels, further supporting the connection between TDP-43 and miRNA biogenesis [188]. More specifically, follow-up studies have confirmed that TDP-43 depletion can lead to altered expression of various miRNAs, such as let-7b, miR-663, miR-9, miR1/miR206, miR-520, miR-132, miR-143, miR-574, and miR-NID1 [210–215].
– As already mentioned, FUS was also found to localize at the Drosha complex together with TDP-43 [207], and further studies have shown that this protein is able to recruit Drosha at chromatin sites of active transcription to promote pri-miRNA processing [216]. Like TDP-43, FUS depletion in human neuroblastoma cells can alter the expression of a consistent number of analyzed miRNAs that include miR-9, miR-125b, and miR-132, which have important roles in neuronal metabolism and differentiation [216]. In the future, the challenge will be to better characterize the extent to which the TDP-43- and FUS-mediated control of miRNA expression contributes to the pathology and whether this may be targeted by specific therapeutic approaches.
– *lncRNA expression*. It is now clear that lncRNA expression is associated with the occurrence of age-related diseases and neurodegenerative disorders [217, 218]. Just like protein-coding RNAs, TDP-43 has been shown to bind and affect the expression of a variety of lncRNAs, such as *gadd7* [219], *SPA* [220], *MALAT1* [181, 221], *NEAT1_2* [181], *Xist* [222], Myolinc [223], and *lncLSTR* [224]. Alterations in the expression for some of these transcripts were detected in human FTLD brains compared to healthy controls [181] or in the spinal motoneurons of sporadic ALS patients (Nishimoto et al., 2013). Interestingly, the regulation of lncRNAs by TDP-43 is not unidirectional, because a recent study has shown that the lncRNAs known as *MIAT* can regulate TDP-43 expression [225].
– Compared to TDP-43, FUS was found to bind to a consistent fraction (30%) of all literature annotated lncRNAs, including NEAT1_2, although not in the same place as TDP-43 [198, 226]. In keeping with this finding, transcriptomic analyses of mouse embryonic stem cells derived from a FUS-ALS model showed that several lncRNAs were misregulated and potentially connected with disease [227]. Finally, as with TDP-43, it has also been reported that lncRNAs such as *hsrw* can rescue FUS toxicity in a *Drosophila* model [228], thus showing that TDP-43 and FUS influence on lncRNAs goes both ways.
– In conclusion, although a direct interaction of FUS and TDP-43 with several lncRNAs has been established, there are still many open questions that remain, such as whether these factors can affect their transcription or stability, how they can act to affect lncRNA biologi-

cal properties, and what is their importance in disease [226, 229]. All these questions will need to be addressed before attempting any therapeutic strategy.

– *ncRNA expression*. In addition to binding with miRNAs and lncRNAs, TDP-43 has also been shown to bind other members of the noncoding RNA family (ncRNAs) [230]. Indeed, in-depth analysis of RNA sequencing data has shown that TDP-43 can bind to several kinds of transcripts such as SINE, LINE, and LTRs [231], and more recent evidence has highlighted in a *Drosophila* model that TDP-43 pathology leads to inhibition of all those mechanisms that are responsible for retrotransposon repression [155]. At the moment, however, the importance of these interactions in disease is not known. As a consequence, their therapeutic potential is also uncertain in the absence of further investigations.
– *Nucleocytoplasmic transport.*Defects in this process have been investigated as potentially responsible for inducing the aggregation process because they might lead directly to abnormal accumulation of TDP-43 and FUS in a specific cellular compartment [232]. Indeed, both TDP-43 and FUS continuously shuttle between the nucleus and the cytoplasm through several receptors such as Transportin-1 (Importin-β2) for FUS and Importin-β1 for TDP-43 [233, 234]. At the molecular level, transport and aggregation of FUS is modulated by arginine methylation of the RGG domain by PRMT1 which reduces binding to Transportin-1 [235–238].
– More recently, nucleocytoplasmic transport has also been linked with ALS/FTLD as part of the possible pathological role played by poly(GA) dipeptides produced from the expanded C9orf72 repeats [239]. Likewise, aggregated and disease-linked mutant TDP-43 have been recently associated with the direct sequestration and/or mislocalization of nucleoporins and transport factors in a variety of disease models, suggesting that disruption of RNA and protein import/export might represent a common feature of ALS disease [240]. Taken together, all this emerging evidence suggests that small molecules able to rescue or prevent these transport defects may be effective for disease treatment.
– *mRNA stability.* Among the genes that play important roles in neuronal viability, such as microtubule dynamics and protein aggregation turnover, TDP-43 has been shown to affect the mRNA stability of the human low molecular weight neurofilament (*hNFL*) [241] and the histone deacetylase *HDAC6* transcripts [242, 243]. However, the list of mRNAs whose stability is controlled by TDP-43 is probably much longer if we take into account that TDP-43 binding regions are particularly abundant in the 3'UTR region of mature mRNAs [72, 244]. As a result, several targets have been described so far, such as *Add2* [245], *VEGFA* and *GRN* [72], and *IL-6* [246], Tbc1d1 [247], and G3BP [248]. In particular, the regulation of G3BP may be very important for neurodegeneration because this protein factor is a component of stress granules (SG) that play a key role in the TDP-43 protein aggregation process [41, 132, 249]. Another direct connection between mRNA stability and disease has come from the recent observation that TDP-43 can suppress Tau expression by promoting mRNA instability, thus suggesting that downregulation of TDP-43 may affect pathology in Alzheimer's disease patients and related Tau pathologies [250].
– Like TDP-43, several studies have reported the binding of FUS to the 3'UTR sequence of many target mRNAs [69, 72, 93, 198]. In particular, FUS depletion in primary cortical neurons has been shown to downregulate the AMPA receptor GluA1 protein subunit by acting on its mRNA stability [251].
– As with pre-mRNA splicing events, the importance of these studies for therapy will depend on the identification of key transcript alterations that could be corrected by RNA therapy.
– *mRNA transport.* As expected, mRNA transport into axons and dendrites is very important to maintain neuronal activity and synaptic plasticity [252]. The first experimental evi-

dence that TDP-43 is important for mRNA transport was first provided by Fallini et al., who showed that in motor neurons TDP-43 co-localizes with other well-known transport RBPs, including SMN and FMRP, and is actively transported along axons [253] in a bidirectional movement [85]. The fact that in the adult mouse brain TDP-43 has been found to bind many mRNAs from synaptic genes has further strengthened a role of TDP-43 in regulating the transport of synaptic mRNAs into distal processes [254].

- Regarding FUS, this protein has also been shown to participate in RNA granule transport into dendrites and in the regulation of local translation at the synapse [255, 256]. In primary hippocampal neurons, FUS can regulate spine remodeling following mGluR5 activation [257] and is transported into dendrites with actin filaments myosin-V whose role is to specifically sort RNA granules into dendrites [255, 258]. More recently, FUS/TLS, TDP-43, and SOD1 have also been shown to be transported to neurite terminals by a mechanism that involves endoplasmic reticulum tubules and the neurofilament cytoskeleton [259].
- *mRNA translation.* With regard to neurodegeneration, mRNA translation is strictly coupled with the process of mRNA transport. The importance of TDP-43 in regulating local translation was first demonstrated in rat hippocampal neurons where TDP-43 was found to act as a translational repressor [260]. This observation was in keeping with several proteomic analyses which identified TDP-43 as mostly associated with the RNA splicing and translation machineries [261]. Subsequently, TDP-43 was also found associated with the heavy polysome fractions [31], and several specific targets regulated by TDP-43 at the translational level have been described: *futsch*/Map 1b, Rac1, MTHFSD, and DDX58 [32, 33, 262–264]. Finally, at the protein interaction level, TDP-43 has been shown to interact with the protein RACK1 that is a known regulator for activity-dependent translation [265] and by regulating the splicing of ribosomal S6 kinase 1 (S6K1) Aly/REF-like target (SKAR) that plays a role in the pioneering round of translation [34].
- Similarly to TDP-43, FUS involvement in controlling local translation was suggested when it was found that this protein can co-localize with APC protein in ribonucleoprotein complexes and promote translation of associated mRNAs, such as *Kank2*, *Pkp4*, and *Ddr2* [266]. Moreover, it has been recently established that mutant FUS proteins can suppress translation by sequestering components of the cellular translational machinery in inclusions [267].
- *Autophagy/lysosome system*. The altered clearance of misfolded or aggregated proteins through the autophagy-lysosome system or the ubiquitin-lysosome system probably represents one of the major causative pathways for ALS/FTLD [268, 269]. First of all, this conclusion is based on the occurrence of mutations in several genes encoding for proteins controlling these pathways, such as *VCP* (autophagosome-autolysosome maturation), *CHMP2B* (late-stage endosome-lysosome fusion), *TBK1* (phosphorylation of autophagy adaptors p62 and OPTN), *OPTN* (autophagosome formation and maturation), and *p62/SQSTM1* (autophagy receptor). In particular, the gene that seems to play a key role is *UBQLN2* (recruitment of autophagosomes to polyubiquitinated aggregates) that may represent a promising therapeutic target [270]. Their detection in patients means that their correct function is closely associated with disease development [268, 271, 272]. Unsurprisingly, impairment of degraded or misfolded proteins is likely to induce pathological aggregation [187, 273, 274]. Moreover, both TDP-43 and FUS have been shown to affect directly the expression of key autophagic/lysosome machinery components either when knocked-down, overexpressed, or in the presence of disease-associated mutations [275–278].
- At the moment, therefore, autophagy and the lysosomal system is considered a primary therapeutic target to preserve neuronal functional-

ity, and several trials are currently under way with autophagy-inducing molecules such as rapamycin, trehalose, and other compounds that have proved to be effective in improving various aspects of TDP-43 and FUS pathology in mouse and cellular models [279–283]. However, it should be noted that many of the approaches tried until now have mainly focused on the role of autophagy in neurons and there is still considerable room for improvement, for example, in better understanding the role played by autophagy dysfunctions in glia cells that make up a considerable amount of nonneuronal cells in our brains [284].

– *Synaptic functions.* One conclusion of all the high-throughput studies that have been performed on identifying the RNA targets of TDP-43 and FUS has shown that many could be affecting synaptic transmission and plasticity [285], an event that could be closely linked with the early motor and cognitive deficits in ALS and FTD [286]. This is supported by several lines of evidence that indicate how overexpression of TDP-43 can impair presynaptic integrity [287, 288], both following disease onset and also at the presymptomatic stage [289, 290]. The connection between synapses and TDP-43 is probably a very conserved evolutionary feature because synaptic control by TDP-43 has been shown to be present also in *Drosophila* and zebrafish disease models [291, 292]. Very similarly to TDP-43, also for FUS, it has been described that missense mutations can profoundly disrupt synaptic homeostasis in a mouse model of disease [293] possibly by affecting mRNA stability of molecules such as SynGAPα2 that promotes maturation of dendritic spines [294]. At present, no therapeutic approaches have specifically targeted this particular aspect of the pathology. However, if we consider the increasing evidence that both TDP-43 and FUS may control synaptic integrity and function, it is likely that this possibility will draw more attention in the future.

TDP-43 and FUS Spreading in ALS/FTLD Diseases

Another important question about TDP-43 and FUS pathology is represented by understanding the mechanisms at the basis of the spread of the disease between different neurons and brain regions [295–297]. In recent years, the hypothesis that has gained most attention is represented by the possibility that TDP-43, FUS, and some polypeptides derived from C9orf72 may spread in a manner that resembles the prion protein [298, 299]. The importance of better understanding if and how these aggregates spread is quite self-evident, because giving an answer to this mechanism may represent a very good therapeutic target. At the structural level, the prion-like spreading hypothesis is supported by the presence of a prion-like domain in the C-terminus of TDP-43 (residues 274–414) and in the FUS N-terminus (residues 1–239) [300]. At the experimental level, support has also come from the observation that in vitro TDP-43 aggregates can induce endogenous TDP-43 aggregation when transduced in HEK293T cells [301] and SH-SY5Y neuronal cells [302]. In parallel, it has also been reported that TDP-43 oligomers can spread from cell to cell by microvesicle/exosome pathways [303, 304] and that TDP-43 aggregates are able to gain entry into cells by stimulating "membrane ruffling" and consequent macropinocytosis [305].

At the moment, the research on FUS is not as advanced as with TDP-43. Nonetheless, a study using a mutant FUS protein that is prone to form fibrils has shown that also this protein has the capability of seeding wild-type FUS [306]. These preliminary results, therefore, suggest that FUS protein may therefore spread between cells using a similar mechanism.

Clearly, TDP-43 and FUS spreading is a very promising area of research because being able to inhibit spreading could obviously represent a very effective therapy. However, there are still many open questions with regard to what are the specific propagating protein assemblies and/or conformations that make this spreading possible. For obvious reasons, finding answers to these questions is an absolute requirement to develop effective therapies.

Modifiers of TDP-43 and FUS Toxicity

Although both TDP-43 and FUS are able to act together to enhance neurodegenerative phenotypes [307], comparative analyses in *Drosophila* and zebrafish models indicate that FUS acts downstream with respect to TDP-43 [308, 309]. This property, however, does not seem to be linked with toxicity as high-throughput approaches to find yeast modifiers of TDP-43 and FUS/TLS toxicity have uncovered that they are quite different from each other [310]. This finding has not discouraged research in this area, and, at the moment, there are several modifiers of TDP-43 pathology that include hnRNP U and hnRNP A1/A2 [311], hnRNP K [312], DAZAP1 [313], ataxin-2 [314], and hUPF1 [315]. At a more general level, it has also been recently reported that upregulation of glycolysis can be induced by overexpression of the GLUT-3 protein in neurons and that this event can be neuroprotective against defects induced by TDP-43 [316]. Likewise, it has also been recently reported that upregulation of the Atg7 gene (a key regulator of macroautophagy/autophagy) can improve motor function and life span in flies that lack *TBPH*, the homologue gene of human TDP-43 [317].

In the case of FUS, it has also been shown that downregulation of several nuclear transport proteins such as Nup154 and XPO1 can prevent FUS-induced neurotoxicity [318] and that muscleblind protein can also rescue FUS-induced motor dysfunctions although in this case the molecular mechanism is still unknown [319]. Finally, it is also interesting to note that some modifiers such as HuR have been reported to act on both TDP-43 and FUS [320], thus showing that contrary to previous expectations, some modifier overlap can presumably exist.

The presence of all these modifiers is quite interesting from several points of view. First of all, many of them could be useful to explain the huge variability that is observed in the age of onset and disease course of TDP-43 and FUS proteinopathies. Secondly, depending on their identity, these modifiers may represent more viable targets for therapeutic action than TDP-43 and FUS. In keeping with this view, it was shown that reduction of ataxin-2 using antisense oligos in a TDP-43 mouse model was able to extend life span and improve the motor phenotype [321].

Conclusions and Future Perspectives

As described in this chapter, the occurrence of TDP-43 and FUS mutations, overexpression, or aggregation can have a profound impact on several important cellular pathways. Although both proteins share many similarities and act on similar pathways [322], they are also quite different according to several lines of neuropathological and experimental evidence [323, 324]. From a therapeutic point of view, therefore, the most important research priority in the future will be to obtain a full understanding of TDP-43 and FUS-controlled pathways to identify those that are mostly responsible for neuronal death (especially at the beginning of the pathology). These targets should then be used to prioritize various RNA-based therapeutic actions that modern technology is currently developing at a very fast pace [23, 325]. Unfortunately, however, both TDP-43 and FUS may not represent ideal "druggable" targets because, as described in this chapter, each of them plays many important and diverse roles within cells. Therefore, altering their general expression within neurons will probably not be very feasible in vivo, as overexpression or downregulation is likely to be considerably toxic. For this reason, a more refined approach would be

that of identifying modifying factors, transcripts, or cellular conditions that might act as suppressors or enhancers of TDP-43 and FUS pathology. An advanced knowledge of these factors/events/conditions will then be useful to identify molecular targets that can be potentially addressed using modern therapeutic strategies. It is only after we have obtained a clear view of many of these still unknown issues that we will probably be able to develop novel, hypothesis-based, therapeutic approaches that could be of clinical benefit.

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A Multi-omics Data Resource for Frontotemporal Dementia Research

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Introduction

Frontotemporal dementia (FTD) is a devastating early-onset dementia characterized by the deterioration of the frontal and temporal lobes, severe changes in social and personal behaviour and blunting of emotions [1]. Up to 40% of cases have a positive family history, and mutations in at least ten genes explain almost 50% of familial cases, and this has been the key to the remarkable progress in our understanding of the molecular basis of FTD. Among the familial cases, mutations in the microtubule-associated protein tau (*MAPT*), granulin (*GRN*) and *C9orf72* are responsible for the majority of cases [2]. Neuropathologically, mutations in *MAPT* are associated with neurofibrillary tangles consisting of hyperphosphorylated tau protein, and mutations in *GRN* and *C9orf72* lead to accumulation of the transactive response DNA-binding protein 43 kDa (TDP-43). Although all three genes are associated with a clinical FTD phenotype, their cellular functions are quite diverse, and how these different genes lead to a similar clinical phenotype is still an unanswered question. Currently, there is no cure for FTD, and for the development of successful therapies, it is essential to understand the role of all genetic and environmental risk factors in the disease process, and to investigate which factors are important in the progression of the disease in all patients and which are specific for subgroups of patients.

It is therefore of utmost importance to identify the regulatory mechanisms that lead to neurodegeneration as a consequence of the already identified mutations and novel genes that are being identified by whole-genome sequencing (WGS) and whole-exome sequencing (WES) studies and genome-wide association studies (GWAS).

Publicly available data resources such as Genotype-Tissue Expression (GTEx) (https://gtexportal.org/home/), Encyclopedia of DNA Elements (ENCODE) [3, 4] and the Functional Annotation of the Mammalian Genome (FANTOM) [5] provide excellent tools to investigate the molecular processes in which identified genes and candidate genes for FTD are involved and can help to determine the processes that regulate the expression of these genes, but an

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important limitation is that all these resources have been generated from human tissues and cellular models of unaffected controls. To understand the role of identified genes in the disease situation, there is a need to generate a publicly available resource from affected cells and tissues obtained from patients and animal models. As part of the European Union (EU) Joint Programme – Neurodegenerative Diseases Research (JPND), we formed the Risk and modifying factors in FTD (RiMod-FTD) consortium with the aim to investigate common and distinctly affected processes in different groups of FTD patients, using a combination of genomic and cell biological approaches on tissues of selected patient groups and corresponding animal and cellular model systems. Our integrative approach allows an unbiased selection of the most suitable targets that can improve our understanding of disease progression and, in addition, will help identify the key genes in the disease process that are the most suitable targets to modify the disease phenotype, and thus provide better choices for therapy development. Here, we describe the current state of our resource and provide examples of how the data can be mined to understand the molecular processes associated with identified genes for FTD and help to prioritize candidate genes identified through WGS/WES and GWAS studies.

The Risk and Modifying Factors in Frontotemporal Dementia Resource

In order to generate a comprehensive multi-omics data resource, we collected frozen post-mortem brain tissue from seven regions (frontal, temporal and occipital lobes, hippocampus, cerebellum, putamen, caudate) of patients carrying mutations in the three most commonly mutated genes in FTD—*MAPT, GRN* and *C9orf72*—and controls without neurological disease for multi-omics characterization. Extensive quality control measures ensured we only included samples that provided us with high-quality ribonucleic acid (RNA), epigenetic and protein data. Because human post-mortem brain represents the disease end stage, we have also collected tissue at different time points of the development of pathology from the frontal lobes of established mouse models for the same three genes. In addition, we have used human immune pluripotent stem (iPS) lines carrying the same mutations, differentiated them into neurons and performed similar analyses. In this way, we have created a resource that can be used to mine molecular data at the end stage of disease but also during life and early differentiation. The inclusion of iPS lines provides us with the additional possibility to investigate and validate identified pathways by targeted perturbation studies with, for example, RNAi and CRISPR-Cas9 (Table 1).

To thoroughly characterize the molecular mechanisms in post-mortem human brain tissue, mouse models and induced pluripotent stem cell (iPSC)-derived neurons, we generated various omics-datasets. RNA-sequencing (RNA-seq), the most widely used omics-technology [6], allows to measure the gene expression of the entire transcriptome, and it thus represents a central dataset in the resource. Additionally, we generated Cap Analysis of Gene Expression sequencing (CAGE-seq) [7] data, which captures the 5′-end of transcripts and can thus be used to profile the transcription start site (TSS) of genes. The CAGE-seq data thus represents a complementary dataset to the RNA-seq data, as it can not only be used to measure gene expression but also to identify different TSS or promoter usage as well as enhancers [8]. The transcriptome is heavily influenced by the epigenome, for instance, by CpG methylation [9]. To assess potential epigenomic changes in FTD, and to help explain observed transcriptomic aberrations, we profiled over 800,000 CpG sites for methylation. Since for all protein-coding genes, the end-product of gene expression is a protein, we used proteomics technology to quantify the expression of thousands of proteins as an important complementary readout to the transcriptome. As both gene expression and translation are regulated, in part, by micro RNAs (miRNAs), we performed small RNA-sequencing (smRNA-seq) to identify important regulator miRNAs and potentially explain

Table 1 List of datasets that have already been generated and processed for RiMod-FTD

Post-mortem human brain tissue		
Data type	Brain region	Samples (control, MAPT, GRN, C9orf72, sporadic)
RNA-seq	Frontal	47 (16, 11, 7, 13, 0)
CAGE-seq	Frontal, temporal, caudate, hippocampus, occipital, cerebellum, and putamen	248 (66, 61, 42, 53, 24)
smRNA-seq	Frontal and temporal	87 (27, 25, 14, 21, 0)
Proteomics	Frontal and temporal	69 (16, 24, 12, 17, 0)
Methylation	Frontal	48 (14, 13, 7, 14, 0)
ChIP-seq H3K4me3	Frontal	16 (4, 4, 4, 4, 0)
ChIP-seq H3K4me3	Sorted neurons (frontal)	25 (8, 8, 3, 6, 0)
Mouse models		
Data type	**Model Mouse line**	**Samples**
CAGE-seq	MAPT-P301L rTg(TauP301L)4510	32 (control: 16, transgenic: 16)
CAGE-seq	GRN knockout $Grn^{tm1.1Pvd}$	33 (control: 17, knockout: 16)
CAGE-seq	C9orf72 knockdown C57BL/6j-Tg(C9orf72_i3)112Lutzy/J	29 (WT: 12, scramble: 9, knockdown: 8)
Proteomics	MAPT-P301L rTg(TauP301L)4510	33 (control: 16, transgenic: 17)
Proteomics	GRN knockout $Grn^{tm1.1Pvd}$	33 (control: 17, knockout: 16)
Proteomics	C9orf72 knockdown C57BL/6j-Tg(C9orf72_i3)112Lutzy/J	31 (WT: 12, scramble: 9, knockdown: 10)
iPSC-derived cells		
Data type	**Cell type**	**Samples (control, MAPT, GRN, C9orf72)**
smRNA-seq	Neurons	21 (9, 7, 4, 6)

changes observed in the transcriptome or proteome. Finally, Chromatin Immuno-Precipitation sequencing (ChIP-seq) was performed for the H3K4me3 protein to identify active promoters. All the above-mentioned genomics data types that have been generated for the RiMod-FTD resource focus on different parts of the cellular transcriptional machinery. By combining these different datasets, it is possible to generate better hypotheses about the disease-causing regulatory mechanisms or to validate existing hypotheses using multiple data modalities. A graphical overview of the datasets already generated and planned for future releases is depicted in Fig. 1.

Analysing Multi-omics Datasets

Generating a multi-omics data resource is, of course, only the first step on the path to gain new knowledge about the condition of interest. The next step is to rigorously analyse the data and/or integrate it with genetic data to generate new hypotheses about disease mechanisms. For large and complex datasets such as those found in a multi-omics data resource, there exists a plethora of bioinformatics methods that can be applied to gather new information. For conventional techniques like RNA-seq, there are several accessible and established tools. For others, the researchers might have to write new algorithms themselves. In recent years, specialized algorithms have been developed that allow the integration of multiple experiments from different technologies [10]. Combining the different datasets with the possibilities of modern bioinformatics can then lead to new insights. Moreover, having a central disease-specific data resource available is beneficial in more ways than just to create new insights based on the resource datasets alone. It depicts a valuable asset that FTD-researchers can use to better interpret their own experiments or test their hypotheses. For instance, a clinician or biologist may state a hypothesis about the involvement of a new gene in FTD pathology based on results from an experiment. Before investing more resources in further investigating the role of this gene, the researcher would like to see some more

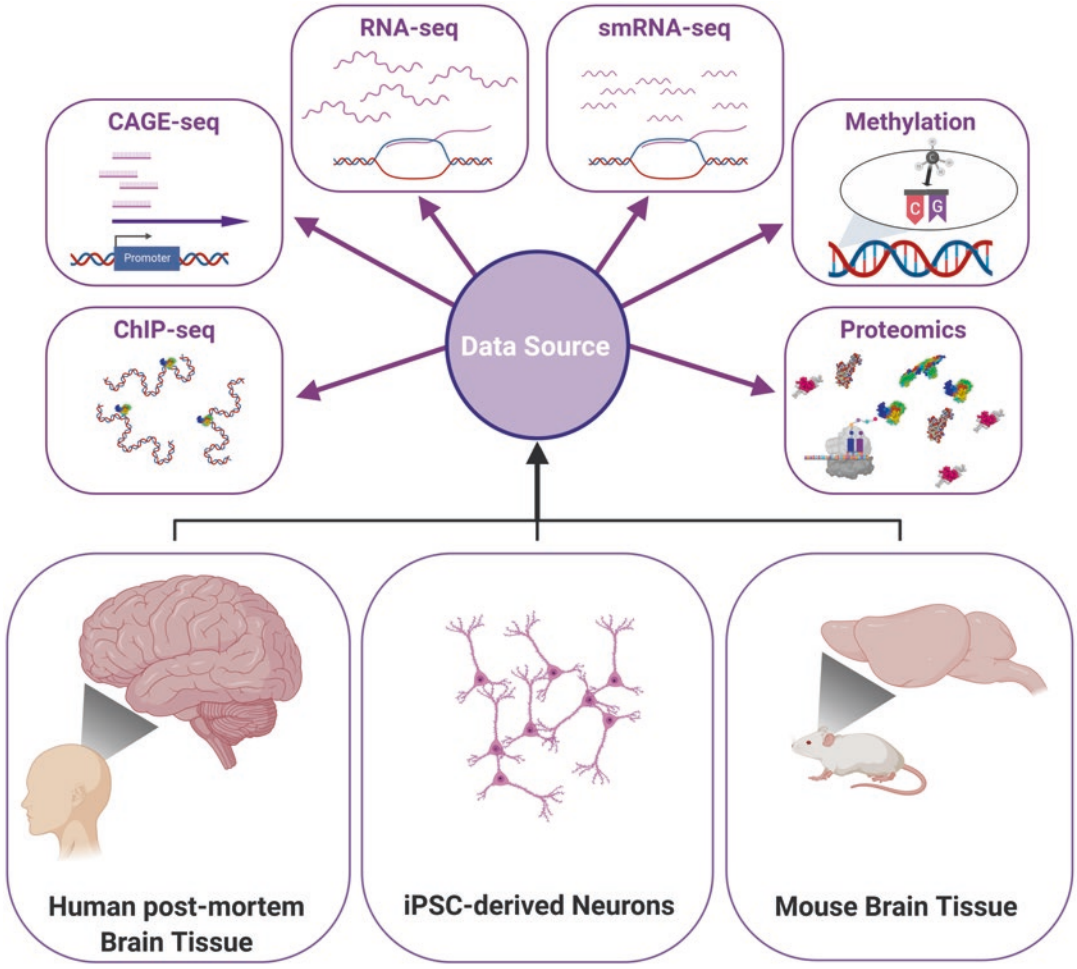

Fig. 1 The RiMod-FTD data resource consists of datasets generated from post-mortem human brain tissue, iPSC-derived neurons and brain tissue from mouse models covering FTD caused by MAPT, GRN and C9orf72. The multi-omics technologies used to generate the data cover ChIP-seq, CAGE-seq, RNA-seq, smRNA-seq, epigenetic arrays and proteomics

evidence. In such a case, RiMod-FTD allows to quickly check the transcriptional state of this gene in several FTD subtypes or whether the quantities of the protein product are changed in the disease. Additionally, the researcher could examine whether the gene is differentially methylated and, finally, check whether aberrant regulation of the gene can be observed in multiple model systems. With more datasets added to the resource in the future, the possibilities for validating experimental results will further increase. Being able to validate scientific findings from own experiments in public data is obviously of great value and helps to identify the best research paths to pursue and thus to accelerate the scientific progress. In the following, we cover the different technologies used to generate the datasets found in the resource, how these data can be analysed and, where suitable, we present some examples related to FTD.

Pre-processing

Before any dataset generated in the wet lab can be mined for interesting results, it first has to be processed and brought into a format suitable for analysis. While great efforts have been undertaken

to simplify this part of the analysis, it remains a very crucial and important step in bioinformatics. The process of converting the raw data that come, for instance, from a sequencing machine, into interpretable and biologically meaningful data points usually requires several steps, each of which is executed with a specialized algorithm. This sequence of steps is commonly called a processing or analysis pipeline. Writing such a pipeline for any omics-data type requires extensive technical knowledge about the data-generating process as well as a good understanding of bioinformatics algorithms capable of handling the respective data. All datasets in RiMod-FTD have been processed and analysed carefully and are available in raw data as well as processed data format. This makes the data more accessible for scientists without extensive domain knowledge, while preserving the raw data for any scientist who wants to process the data with a different pipeline.

Analysing the Transcriptome with Ribonucleic Acid Sequencing

The transcriptome is probably the most commonly studied 'ome' and plays a central role in many studies. Rightfully so, as regulation of gene expression underlies most cellular processes, it is aberrant in many diseases and depicts the closest readout for effects from genetic and epigenetic variation. While multiple technologies exist that can measure gene expression, RNA-seq is the most common one nowadays. Because of this, and because of the importance of the transcriptome, excellent tools exist that help to analyse RNA-seq data. Usually analysis of transcriptomic starts with identifying differentially expressed genes (DEGs) between different groups of samples. Several software packages for this purpose, called differential expression (DE) analysis, exist, such as DESeq [11] or edgeR [12], which allow to apply carefully developed statistical models to calculate fold-changes and *p*-values for every gene. Although DE analysis is a very standard approach and the above-mentioned software packages are easy to use, care must be taken by the user to specify the design matrix correctly and to account for confounding variables such as age, gender or experiment batches. The results of DE analysis constitute the basics of many downstream methods and help the experimenter to identify pathways that are most affected by a condition. Along with raw RNA-seq data, the RiMod-FTD resource contains pre-calculated fold-changes and *p*-values for the most important comparisons of the contained transcriptomic datasets. This makes it easy to quickly check the status of a specific gene in multiple FTD subgroups or model systems, without the need to first process and analyse the data.

The entire set of DEGs defined by DE analysis can be used in combination with public databases of pathways and gene sets that have been curated by experts to test for enrichment of DEGs in some of these pathways. Results from such analyses can be of great value, as they, if done correctly, immediately highlight the cellular processes different between conditions. In a recent study, Dickson et al. [13] performed RNA-sequencing on human brain samples of patients with *C9orf72* repeat expansion, patients without this mutation and control subjects. Using pathway analysis in combination with weighted gene co-expression network analysis (WGCNA), they found that vesicular transport pathways are especially affected by *C9orf72* repeat expansions. Using only transcriptomic data, the authors could highlight several affected pathways in *C9orf72* mutation carriers and identified biomarker candidate genes by applying LASSO regression. Importantly, RiMod-FTD contains datasets from patients not only with *C9orf72* but also with *GRN* and *MAPT* mutations, and it thus allows to test for commonalities between the disease subgroups in terms of affected pathways or WGCNA modules. For example, analysing the RNA-seq data from the RiMod-FTD resource, we have found that oxidative phosphorylation is impaired in both FTD-*GRN* and FTD-*MAPT*. However, membrane-trafficking-associated pathways appear to be strongly down-regulated in FTD-*MAPT*, while FTD-*GRN* shows a stronger enrichment for immune system–related pathways. Moreover, as lists of affected pathways are available in the resource, a scientist with an interest in a specific pathway can quickly investigate

whether this pathway is affected in some FTD subtype or model system.

Complex tissue, like post-mortem brain tissue, consists of several transcriptionally different cell types. When interpreting RNA-seq experiments on such tissues, it is important to keep in mind that systematic differences in cell-type compositions between sample groups can lead to false-positive DEGs in the analysis. To account for this problem, several cell deconvolution methods have been developed that allow to estimate the cellular composition of each sample from RNA-seq data. Not only does this help to control for false positives, but it can also uncover unknown cellular composition changes in a disease. Examples for cell deconvolution algorithms are MuSiC [14] and Scaden [15]. The latter has been developed for the analysis of data from the RiMod-FTD project and showed best performance on post-mortem brain tissue when compared to other algorithms.

Co-expression Analysis

If an expression dataset is sufficiently large, gene co-expression analysis can be used to obtain dataset-specific expression modules that are relevant to the disease. WGCNA, which was mentioned earlier, is the most popular algorithm for this task [16]. Briefly, WGCNA calculates co-expression values of genes across a dataset, which can then be used to cluster genes into co-expression modules. The underlying assumption is that genes with similar expression patterns tend to have similar functions or are involved in overlapping regulatory mechanisms. A module eigengene, which is the first principal component of the expression matrix, can be used to associate traits with modules—which allows to identify disease-associated modules. Other, module-internal metrics calculated by WGCNA help to identify module hub-genes that might be of special importance. In the study mentioned earlier by Dickson et al., WGCNA was used to identify co-expression modules that are associated with the *C9orf72* repeat expansion. Through module analysis, they identified a module that contained the gene *C9orf72* and was enriched for metabolic pathways, indicating that *C9orf72* might have a similar function or affect these pathways. Another study from Swarup and colleagues [17] performed WGCNA on RNA-seq data from brain tissue of mouse models for *MAPT* and *GRN* mutations. The authors identified two modules that are significantly correlated with tau hyperphosphorylation, a marker of disease progression in FTD and Alzheimer's disease (AD) [18]. By further analysing these modules, they were able to highlight multiple genes with potentially important roles in the pathways represented by the modules. These studies show how valuable information can be extracted from transcriptomic data alone using pathway- and module-based approaches. A great advantage of RiMod-FTD is the availability of transcriptomics datasets from several tissues and model systems. This allows us to evaluate the robustness of co-expression modules—which are often to some extent dataset-specific—longitudinally and across different model systems. Furthermore, modules or pathways that a researcher has identified in their own dataset can be tested for reproducibility in the various FTD-related datasets of RiMod-FTD. We believe that lacking reproducibility of results generated with genomics technologies is a major hurdle to the scientific progress, and public resources with easily accessible datasets like RiMod-FTD are one way of addressing this problem.

Alternative Splicing of Transcripts

While it is common to perform most analyses with RNA-seq data on the gene level, it is possible to infer transcript-level information from this data as well. However, estimating transcript abundances from RNA-seq data is substantially more challenging, as the sequence of isoforms overlaps to a large part, and, consequently, most reads could be assigned to multiple transcripts. Furthermore, the downstream analysis options are currently not as rich for transcripts as for genes, since many tools (e.g. pathway databases) operate mainly on the gene level. Nevertheless, various tools for the quantification of transcripts and the detection of alternative splicing have been developed. For instance, Leafcutter and MAJIQ are two modern examples of algorithms

that can identify alternative splicing events from RNA-seq data [19, 20]. Both tools circumvent the problem of transcript quantification by focusing on exon splice junctions, and thus the exclusion of introns, instead of the inclusion of exons [19]. Although differential splicing analysis is still not routinely done with RNA-seq data, it has long been known that aberrant splicing can have devastating effects and lead to disease. For instance, the authors of MAJIQ reported differential splicing of the *CAM2K* gene in Alzheimer's disease (AD) [20]. The gene *MAPT* is another prominent example. Mutations in *MAPT* lead to a ratio change of tau isoforms, the protein product of the gene. The isoforms have different chemical properties, and the disrupted balance between them can cause disease [21]. Mutations in the genes for TDP-43 and FUS have been associated with alternative splicing in amyotrophic lateral sclerosis (ALS) [22, 23], and a mutation in the gene *PINK1* was shown to activate a cryptic splice-site in Parkinson's disease [24]. Many other mutations can cause alterations in splicing and cause disease, showing that the interrogation of differential splicing represents an important aspect of RNA-seq data analysis. The RNA-seq datasets in the RiMod-FTD resource have been analysed for alternative splicing and can be easily queried for evidence of alternative splicing of a gene of interest in a specific FTD subgroup. Transcriptomic regulation via alternative splicing is a complex mechanism that certainly has not been fully interrogated, and we hope that the diverse RNA-seq data available in RiMod-FTD can help to elucidate the role of gene isoforms in FTD.

Detecting Regulatory Mechanisms

Once deregulated cellular pathways in a disease have been identified using methods such as DE analysis, pathway enrichment or WGCNA, it is often of great interest to identify the regulatory mechanisms that drive these changes. Indeed, this depicts the major goal of many studies. Understanding the regulatory mechanisms that underlie a disease greatly helps to identify druggable targets that can be further interrogated and potentially help to develop treatments. However, the regulation of the transcriptome involves numerous players that work with and against each other, and no single assay can capture all of them. Therefore, a multi-omics approach is essential. The great advantage of RiMod-FTD is that it contains multi-omics datasets from matching samples, which measure different aspects of transcriptomic regulation. This makes it possible to identify potential regulatory mechanisms or confirm or deny hypotheses about transcriptomic regulation. In the following, we cover different modes of regulation, assays available in RiMod-FTD that can be used to understand them and bioinformatics algorithms that help to extract the desired information.

Regulation by Transcription Factors

The most well-known players in the regulation of gene expression are transcription factors (TFs), which bind to promoters and can increase or repress the expression of one or several genes. Multiple bioinformatics tools have been developed to identify candidate TFs responsible for observed expression patterns. They differ in the data that they require as input and the information they use to generate TF rankings. One method to identify active TFs is to look for enrichment of transcription factor binding sites (TFBS) in the promotor region of a set of genes compared to a background. CAGEd-oPOSSUM [25] uses user-provided CAGE-seq data to generate promoter-proximal regions, which are then scanned for TFBS enrichment. Promoters, which are often in the vicinity of the TSS, are thus frequently enriched in the region around CAGE-peaks. A different approach is taken by ChEA3, which only needs a list of genes as input [26]. The algorithm then integrates information gathered from various sources to rank TFs according to consistent evidence across information sources. As this approach only relies on a list of, for example, up-regulated genes, which can be readily inferred from RNA-seq data, it is widely applicable. Because RiMod-FTD contains both CAGE-seq and RNA-seq data, both above-discussed methods can be applied, in complementary fashion, to the data. Chromatin Immunoprecipitation sequencing (ChIP-seq) is

another technology that can be used to study regulation by TFs [27]. With ChIP-seq, the experimenter can identify DNA elements to which a protein of interest binds. As TFs bind to DNA, a ChIP-seq experiment for a particular TF will identify promoters and enhancers that are bound by the TF of interest, which can be used to identify genes regulated by these promoters. The analysis of ChIP-seq data requires specialized algorithms that discriminate between real binding sites and background signal. A very popular tool for this purpose is MACS2 [28]. Although RiMod-FTD currently does not contain ChIP-seq data for specific transcription factors, it contains H3K4me3 ChIP-seq data. H3K4me3 is associated with active promoters and can thus be used to identify active genes and TFs that potentially drive the expression (similar to CAGE-seq). In addition to RNA-seq, CAGE-seq and ChIP-seq, RiMod-FTD also contains proteomic data that can be assessed for TF quantities, which give a more direct readout than using mRNA levels as proxy. However, on a more cautious note, we want to mention that TFs are usually of low abundance in the cell and are thus not always caught by proteomics experiments [29]. It is thus important to use all available datasets for inferring relevant TFs.

Regulation by Micro-RNAs

Micro-RNAs (miRNAs) are another type of important transcriptional regulator that mainly works by binding to the 3′-end of messenger RNAs (mRNAs) to decrease the mRNA stability or to repress the rate of translation [30]. Hence, they affect both the abundance of mRNA and the rate of protein production. Because miRNAs are very short (21–25 nucleotides), specialized protocols must be used for miRNA expression profiling, which is why their activity cannot reliably be inferred from a typical RNA-seq experiment, which measures mRNA or total RNA expression. RiMod-FTD contains smRNA-seq and RNA-seq data from matched samples. This is of great value, as it allows to identify potential miRNA-target pairings with greater confidence. First, candidate targets for each miRNA are predicted, a task for which several computational tools have been developed. These algorithms incorporate knowledge about miRNA-biology, such as the seed sequence of miRNAs—which must be complementary to a region in the target gene—or evolutionary information. However, as the seed regions used for binding to targets are very small, computationally predicted targets contain high numbers of false positives [31]. Paired information of gene and miRNA expression can be used to perform correlation analysis of miRNA-target pairs [32]. The assumption here is that a negative correlation should be observed when the miRNA regulates a target candidate. If no negative correlation is observed, then either the target prediction is wrong or the regulation by the miRNA is overshadowed by other regulatory effects.

As an example for this approach, we want to highlight a study by Swarup and colleagues, where the authors used protein coding gene and miRNA expression data to identify the miRNA—miR-203—as a potential regulator for a disease-associated co-expression module in mouse models of FTD [17]. After highlighting this miRNA as a potential regulator, the authors went further and overexpressed this miRNA in mouse neuronal cell cultures, where they could observe down-regulation of the predicted targets along with increased apoptosis, thus validating their findings from the transcriptomic data. Replication of such candidate miRNAs in other datasets is important. The RiMod-FTD resource contains several datasets of matched gene- and miRNA-expression, which can be used to infer potentially important regulator miRNAs or to validate findings from other studies, such as those from Swarup et al.

Regulation by Deoxyribonucleic Acid Methylation

The methylation of DNA residues can have strong regulatory effects on gene expression. Cytosine residues can be methylated at their fifth carbon molecule, usually in the context of CpG dinucleotides [9]. CpG methylation at the promoter of genes causes transcriptional repression of that gene. Aberrant methylation can therefore directly affect the transcriptome, and many human diseases have now been associated with

methylation [33]. Many technologies for measuring DNA methylation exist, of which methylation array chips are a popular method that nowadays cover over 850,000 different CpG sites across the genome. Specialized software packages have been developed to analyse this data. Like DE analysis, differentially methylated CpG sites between two conditions can be inferred. RiMod-FTD contains methylation data of the newest technology, covering over 850,000 different CpG sites. These data serve as an additional resource for identifying underlying regulatory mechanisms and can help to elucidate disease-related changes in the epigenome. As an example for the relevance of DNA methylation in FTD, repeat expansions in the *C9orf72* gene—a common cause of FTD and ALS—are associated with hypermethylation of the repeat itself and *C9orf72*-flanking CpG island [34]. Gijselinck and colleagues reported that the repeat size correlates with the degree of hypermethylation, with longer repeats leading to more methylation of the flanking CpG island [35]. Repeat size and methylation state are also correlated with age at onset, and the authors suggested that the increased methylation might be a factor explaining the differences in age at onset of the disease.

Proteomics

Being the end-product of gene expression, splicing and translation, proteins constitute the major functional molecules in the cell. Although higher gene expression generally leads to higher quantities of the protein product, the correlation of these two quantities varies significantly [36]. Measuring mRNA concentration is hence not enough to infer protein concentrations [37]. It is obvious that the interrogation of the proteome is a fundamentally important step on the path to understanding cellular pathways and diseases that complement transcriptomic and epigenomic profiling. While the mature RNA-seq technology can be readily used to measure the expression of the entire transcriptome, quantification of the proteome depicts a more difficult challenge. The current technology works by digesting proteins into smaller peptides, which are subsequently measured by lipid chromatography (LC) and mass spectrography (MS). Bioinformatic algorithms are then employed, in combination with databases, to translate the quantified peptides into protein-level information [38]. Like gene expression, differences of protein quantities between conditions can then be assessed. In addition to the transcriptomic and regulatory assays, RiMod-FTD contains several proteomics datasets from diverse resources, such as multiple brain tissues, patients with different causal mutations or different mouse models. While these datasets cannot cover the entire transcriptome, they represent valuable complementary measurements that help to examine how transcriptional aberrances translate into the proteome. As proteomics experiments are less often conducted than RNA-seq experiments, we believe that the proteomics datasets of RiMod-FTD will be of especially high value for scientists working in the field.

Advantages of Multi-Model Approaches

As shown earlier, the use of multiple omics technologies to profile a biological system and to understand a disease is of great value. It allows us to study several, albeit not all, parts of the highly interconnected regulatory machine that is the cell and is therefore indispensable for widening the systems-level understanding. However, most diseases, especially neurodegenerative diseases such as FTD, arise through complex mechanisms that lead from disease onset to the final disease stages. Understanding these temporal pathway activity patterns and interactions is essential for a complete understanding of a disease, and most probably necessary to eventually develop remedies. To study neurodegeneration, brain tissue is often used—which is only available post-mortem (with some exceptions) and therefore represents the very end stage of the disease. Especially for diseases that develop over many years, only examining the end stage will not allow us to fully understand how the disease develops. It is therefore crucial to use a multi-model approach to study a complex disease like FTD. For instance, mouse models of neurodegeneration allow to

profile the disease development over different temporal stages [39]. Of course, other ramifications exist for these models, as findings in mice rarely entirely translate to humans, and a mouse disease model never completely recapitulates the actual disease [40]. Nevertheless, they depict a valuable complementary model to human post-mortem brain tissue. To increase the value of using mouse models, modern machine learning–based approaches have been developed that help to translate the findings from mice to humans [41].

A further level of complexity arises when considering the complex multicellular nature of both human and mouse brain tissue. While many cell types are typically affected in neurodegenerative diseases, the dysregulated pathways likely differ from type to type. This has been increasingly recognized in recent years. As an example, microglia have been identified as being a major factor in the development of AD [42]. In addition to tissue-level models, studying specific cell types is therefore necessary to understand the causal mechanisms behind the development of neurodegenerative diseases. In the past decade, several methods have been developed that made it possible to differentiate patient-derived induced pluripotent stem cells (iPSCs) into all the major cell types found in the brain [43]. This makes it possible to study the effects of the patient-specific genetic background on specific cell types, for instance, neurons. IPSC-derived neurons thus represent a valuable approach to study cell type–specific effects under controlled conditions that cannot be examined in complex tissues. Zhang and colleagues differentiated iPSCs derived from a patient with a mutation in the FTD-causing *CHMP2B* gene into cortical neurons, which allowed them to study neuronal-specific effects of this mutation [44]. The authors identified abnormalities in endosomes and mitochondria as the most significant alterations caused by this mutation, providing insights into the causal mechanisms of *CHMP2B* mutations in neurons. The authors of a different study used iPSC-derived neurons from a patient with *MAPT* mutation and identified transcriptional changes of GABA receptor genes, which they verified in other data from mouse modes and human brain tissue [45]. These results show how iPSC-derived neurons can be used to study neuron-specific disease mechanisms that are directly caused by a genetic alteration.

The consideration of the above-mentioned advantages and disadvantages of different model systems and tissues led to the decision to make RiMod-FTD a disease-specific data resource that contains datasets from multiple model systems. Having these multi-model datasets facilitates the discovery of mechanisms that translate from model to model, or tissue to model and enables to derive much more robust hypotheses.

Genetics Analysis

Even though almost 40% of patients with FTD have a positive family history, there exists a large gap of missing heritability to explain close to half of these cases, with the rest carrying mutations in known FTD genes such as *MAPT, GRN* and *C9orf72* [2]. With a massive influx of advancement in genetic methodologies in the past two decades, the scope to identify and study disease-causing mutations has amplified and goes beyond linkage analysis and candidate gene studies. The human genome has 100 million single-nucleotide polymorphisms (SNPs) identified to date, which can quickly and cost-effectively be genotyped using arrays. Genome-wide association studies (GWAS) are a classic example of using genotyped data to compare SNPs between healthy and diseased individuals. Strides in next-generation sequencing have also helped identify novel genetic factors and rare damaging variants implicated in FTD.

Genome-Wide Association Studies

A GWAS is based on the concept of linkage disequilibrium, which allows for a subset of SNPs to be used as proxies to genotype the entire genome. It relies on the 'common variants' theory to identify risk factors with modest effect and, in turn, risk loci in the genome that may be used to identify genes that can be clumped together to confirm pathways and processes relevant to that disease [46]. In the largest FTD-GWAS cohort, to

date, alterations in the immune system, lysosomal and autophagic pathways were identified as associated to FTD risk [47]. Since GWASs rely on finding SNPs with moderate effects, it is important to have large cohorts to be able to achieve enough statistical power to see a true biological effect. This study included a two-stage GWAS (discovery phase and replication phase) for clinical FTD, utilizing samples from 44 international research groups. The most widely used tool for GWAS is PLINK [48, 49].

As a follow-up, they performed expression and methylation quantitative loci analysis to study their effect on the associated SNPs. These types of analyses are frequently clubbed together to help discriminate causation from association as it is an important point of note that while proxy SNPs are associated with traits, they are seldom causative. The RiMod-FTD resource of multi-omic data from different brain regions of FTD patients can be useful in mining the hits found in such large-scale GWAS studies and understand the biology lying underneath the association.

For example, a recent GWAS study, shows that the rs72824905-G allele in the gene PLCG2 is associated with decreased risk in FTD as well as increased changes of longevity [50]. Following up on this finding using the RiMod-FTD RNA-seq data, we found that PLCG2 is up-regulated in patients carrying a *GRN* mutation. Loss of *GRN* function has been associated with elevated microglial neuroinflammation [51]; this finding may lend evidence to the protective effect of PLCG2 in brain immune function.

To verify this link between genes involved in brain immune function analysis and FTD and the mechanism by which they act, integrative analysis involving the results from the different omics data under the RiMod-FTD resource can help utilize the plethora of information that all of these different techniques shed a light on.

Next-Generation Sequencing

Identification of rare variants that play a role in disease progression cannot be accomplished with GWA studies that rely on the 'common variants theory'. Association of rare variants with patient status can be assessed using burden tests using the SNP-set (Sequence) Kernel Association Test (SKAT) [52]. Such tests collapse variants into genetic scores and are extremely powerful at detecting high-impact variants that are causal in the same direction. Other tests that have been used are variance tests and combined variance tests that combine burden and variance tests. These tests rely on estimating the variance of genetic effects to uncover the missing heritability. PLINK can be used to perform all of these different types of tests to elucidate the effects of rare variants in FTD, which are often of higher impact than common variants.

In the FTLD-TDP whole-genome sequencing consortium [53], WGS data from 517 unrelated patients and 838 controls were used as a discovery cohort to perform a gene-level analysis of rare variants. The authors used gene-burden analyses to prioritize 61 genes in which LOF variants were observed in at least three patients. TBK1 showed the most LOF mutation carriers, along with genes involved in the TBK1-immunity pathway. TBK1 LOF mutations are also third most frequent in the Belgian FTD cohort from the BELNEU Consortium [54], after *C9orf72* and *GRN*. While this association has been confirmed by multiple studies, the mechanisms are yet to be confirmed. Using RNA-seq and CAGE-seq data from the RiMod-FTD resource, pathway and gene-set enrichment analysis can be performed to explain the mechanism in which TBK1 mutations implicate patient status for FTD. Interestingly, TBK1, unlike PLCG2 was down-regulated in patients carrying a *GRN* mutation in the RiMod-FTD RNA-seq data. These findings offer an opportunity at a deeper understanding at the mechanism behind these correlations and the potential to uncover therapeutic targets.

Public Resource

The primary goal of RiMod-FTD is to generate a versatile data resource that can help to accelerate and support the field of FTD research. To this end, all datasets generated during the project, accompanied by useful analysis results, are made available at the European Genome-phenome

Archive (EGA) [55]. Additional to making the data available in the central and well-known database EGA, it is our plan to develop a graphical user interface that facilitates to visually inspect the data directly in the browser, without any need to download it or analyse it. This will make RiMod-FTD further accessible, especially for scientists or clinicians who only want to check the expression of a single gene or pathway.

Concluding Remarks and Outlook

An ongoing effort of RiMod-FTD is to increase the number of diverse and useful datasets over time. In addition to completing the set of currently used multi-omics experiments for all tissues and model systems available, other experiments are planned as well. We aim to extend human post-mortem brain samples and mouse models to additional mutations, sporadic cases and spectrum disorders such as progressive supranuclear palsy (PSP) and amyotrophic lateral sclerosis (ALS). We also aim to extend over brain regions to be able to compare strongly affected regions with relatively preserved regions. The development of single-cell approaches and spatial transcriptomics has enabled us to examine changes at single-cell resolution, which is necessary to disentangle the cell-type-specific transcriptomic changes. Adding single-cell experiments to RiMod-FTD will therefore increase the value of the resource. Complementary to single-cell RNA-sequencing (scRNA-seq) approaches, we aim to differentiate patient-derived iPSCs into different relevant cell types, such as microglia and co-cultures. This will be done for additional mutations as well.

With these planned efforts and the already existing data, we hope to further untangle the cellular mechanisms behind the complex disease FTD and believe that the RiMod-FTD resource constitutes a significant contribution to the field of FTD research that will help to accelerate the scientific progress towards better disease understanding, diagnosis and eventually treatment.

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Mendelian and Sporadic FTD: Disease Risk and Avenues from Genetics to Disease Pathways Through In Silico Modelling

Claudia Manzoni and Raffaele Ferrari

Introduction

Complex disorders are by definition non-linear conditions where environmental and genetic factors play an intertwined role in contributing to disease pathogenesis and progression. Environmental factors are challenging in that it is difficult to identify and measure those that specifically impact disease [1]. Conversely, the dissection of genetic factors has benefitted from constant improvements in the technologies for generating high-resolution data and analytical tools (Wetterstrand KA. 2019. https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost).

We have come to appreciate that, on the basis of genetics, there are two broad categories of patients: (i) a minority of so-called familial cases where pathogenic (Mendelian) mutations in single candidate genes (i.e. Mendelian genes) co-segregate with disease and (ii) a majority of so-called sporadic cases where, in the absence of Mendelian mutations, multiple genetic variants with small effect size increase the risk for developing disease.

Mendelian genes have been classically isolated via linkage analysis and/or whole-exome/genome sequencing of trios, first-degree relatives or well-phenotyped pedigrees [2]. Sporadic forms of disease are conveniently investigated through case/control association studies, e.g. genome-wide association studies (GWAS) [3]. The idea that genetic investigation of *familial cases* is straightforward is only apparent. It is, in fact, worth noting that there are uncharacterised *familial cases* where Mendelian mutations have not been isolated [4]. Also, functional investigation of Mendelian genotype-phenotype correlation has proven neither time- nor cost-effective, to date. Moreover, the genetic architecture of risk for *sporadic cases* is challenging to assess and even harder to model, especially considering that multiple variants with small effect size are to be taken into account, simultaneously.

In this chapter, we focus on the heterogeneous features of frontotemporal dementia (FTD) touching upon its complex genetic landscape and discuss how novel approaches (e.g. in silico systems biology) promise to revolutionise the translation of genetic information into functional understanding of disease. These approaches represent a stepping-stone towards functional validation of risk pathways and, possibly, drug target identification. All this holds relevance as the

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field is accelerating towards effective clinical trial design and the development of measures for early diagnosis, disease prevention/monitoring and cure.

FTD and Disease Risk

Environmental Factors

The environmental exposure contributing to FTD pathogenesis is an understudied and complicated matter. It is widely accepted that complex neurodegenerative conditions, including FTD, are influenced by environmental risk factors acting in concert with the genetic risk architecture within a process referred to as gene-environment interaction [5].

No single environmental factor clearly leading to FTD has ever been indicated. Only concepts such as 'cognitive reserve' [6, 7] or 'aging' [8] have been suggested to influence disease risk and modulate age at onset. Additionally, few epidemiological studies highlighted possible links between FTD, cardiovascular disease and diabetes risk factors [9–11].

The environment is believed to influence risk for complex neurodegenerative disorders via, at least, two mechanisms. On the one hand, the environmental exposure (e.g. aging) may modulate methylation profiles in the genome or the activity of non-coding RNAs (ncRNAs) impacting gene expression and influencing disease onset and progression [12, 13]. On the other hand, the environmental exposure can represent the direct mechanistic insult triggering processes that lead to disease. For example, lessons learned from other complex neurodegenerations, such as Parkinson's disease (PD), indicate that certain toxins and pesticides can cause a cascade of effects resulting in oxidative stress that ultimately influences disease pathogenesis [14]. Also, traumatic brain concussions have been implicated in certain forms of dementia (including Alzheimer's disease [AD] and FTD) [15], and it was suggested that physical insults were linked to toxic stress resulting in mitochondria alteration, oxidative stress [16] or amyloid aggregation [17], globally impacting brain homeostasis and, subsequently, disease pathogenesis.

A better understanding of the environmental risk factors playing a role in complex neurodegenerations, such as FTD, would critically complement our dissection of disease biology (e.g. it would help highlighting impacted pathways and molecular mechanisms). A substantial caveat here is represented by the lack of efficient and reliable methods to investigate and measure the environmental exposure(s) that influence and/or contribute to the pathogenesis of complex neurodegenerations. Nevertheless, a promising approach that might aid in closing this critical gap is Mendelian randomisation (MR). MR is a statistical approach where common variants such as single nucleotide polymorphisms (SNPs) that are associated with a certain environmental exposure (e.g. SNPs which increase individual risk/chance of smoking, drinking, developing cardiovascular disease) are used as proxies to assess association with SNPs in the disease under investigation [5]. This approach is still to be explored in FTD, yet it promises to shed light on those environmental exposures that might be relevant to FTD pathogenesis: power issues associated with GWAS performed in FTD have hampered the possibility of performing effective MR studies, to date.

Genetics

In line with its heterogeneous clinical and pathological characteristics (which can be reviewed in [18–20]), FTD's genetic features mirror its complicated global phenotypic picture [21, 22]. A positive familial history, familial (fFTD) or Mendelian, is seen in ~10–30% of cases [23–25], whilst a remainder ~70% of cases, individuals with disease but no clear familial history and/or genetic aetiology, are categorised as *sporadic* (sFTD) [21, 22].

Mendelian FTD

The vast majority (≥25%) of fFTDs associates with pathogenic mutations in *MAPT* [26], *GRN* [27] and *C9orf72* [28, 29], whilst a small minority

(<5%) associates with (very) rare mutations in *CHMP2B* [30, 31], *VCP* [32], *TBK1* [33–35], *IFT74* [36], *OPTN* [35], *SQSTM1* [37], *UBQLN2* [38], *CHCHD10* [39] and *TIA1* [40].

Mutations in *MAPT*, *GRN* and *CHMP2B* have almost exclusively been described in 'pure' FTD cases [21]. In few occasions, issues were raised on whether (all) Mendelian mutations are fully penetrant (e.g. *GRN* mutations have shown to be associated with variable age at onset or a spectrum of phenotypes within the same family [22]). Expansions in *C9orf72* have shown to be ubiquitous across neurodegenerative disease. Although they are most frequently found in cases diagnosed with FTD and amyotrophic lateral sclerosis (ALS) or within the FTD-ALS spectrum, they have also been reported in a range of phenotypes, including AD, Parkinsonian syndromes, Huntington's disease (HD), corticobasal syndrome/degeneration (CBS/D) and non-demented elderly individuals [29, 41–49]. Mutations in the remainder genes have been isolated in small numbers of (at times even single) families displaying substantial syndrome heterogeneity: a complex phenotypic signature characterised by inclusion body myopathy (IBM), Paget's disease of the bone (PDB) and FTD (IBMPFD) for *VCP* [50] and ALS and/or the FTD-ALS spectrum for *SQSTM1*, *UBQLN2*, *IFT74*, *OPTN*, *CHCHD10*, *TBK1* and *TIA1* [21, 22]. Of note, *TARDBP* and *FUS* mutations have been mainly reported in ALS whilst very rarely in FTD cases [51, 52]. It is thus still debated whether or to what extent *TARDBP* and *FUS* are to be considered 'FTD genes' [52, 53] (despite the fact that TDP-43 and FUS are clear pathological hallmarks of FTD [54]).

Regardless of complexity and heterogeneity, a key point is that Mendelian (i.e. for the most, coding) mutations, provided their large effect size, appear to be sufficient to trigger disease. Therefore, although quite rare and exclusive to a (rather small) number of families or private cases, they are indeed informative candidate genes/targets to model disease.

Sporadic FTD

Sporadic FTD cases (sFTDs) are generally screened for known candidate genes: pathogenic variants have been reported in *MAPT*, *GRN*, *C9orf72* or *TBK1* in ≤10% of cases [21, 22, 55, 56]. These might be due to de novo mutations that can (very rarely) occur in the population or (likely) to the fact that they might be cryptic Mendelian cases.

Genetics of sFTD is still poorly understood. Sporadic cases are investigated through GWAS where millions of SNPs are compared across thousands of cases and controls [3]. A GWAS assesses allele frequencies of 'common' genetic markers (SNPs) (i.e. they are present in the general population) in the two sample sets. Those markers that associate with increased risk for disease display a significantly increased frequency in cases when compared to controls. Genetic risk markers identified through GWAS are generally non-coding variants, and they are characterised by small effect sizes; thus, one single SNP is neither necessary nor sufficient to lead to disease [57]. Rather, multiple SNPs cumulatively contribute to disease pathogenesis and represent the so-called genetic architecture of disease (i.e. the genome-wide asset of genetic risk) [58].

To date, a handful of GWAS have been performed in sFTD [4]. GWAS require large cohorts of cases and controls (n = thousands), and this may sometimes represent a drawback (especially when a disease is rare or heterogeneous). In order to cope with sample collection and power issues for genetic studies of sFTD, multicentre initiatives such as the International Frontotemporal Dementia Genomics Consortium (IFGC; https://ifgcsite.wordpress.com/) and the International FTLD-TDP Whole-Genome Sequencing Consortium [56] have been established. Networks of this kind allow to share expertise and collate large numbers of samples across research centres to increase the statistical power of sFTD genetic studies.

The first FTLD-GWAS was published in 2010 by Van Deerlin et al. using a cohort of 604 cases with either pathologically confirmed frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP) or cases carrying a *GRN* mutation (515 discovery phase; 89 replication phase). This study highlighted risk variants at a locus on chromosome 7p21 [59]. Subsequently, a larger GWAS

was published in 2014 by Ferrari et al. using a cohort of 3526 clinically diagnosed sFTD cases (2154 discovery phase; 1372 replication phase) leading to the identification of a risk locus on chromosomes 6p21.3 (for the entire cohort) and a suggestive risk locus on chromosomes 11q14 (for behavioural variant FTD [bvFTD]) [60]. A smaller GWAS was then performed by Ferrari et al. in a population-specific cohort of 530 Italian sFTDs: two suggestive signals were indicated by this study in loci mapping to chromosomes 2p16.3 and 17q25.3 [61].

Genome-wide approaches can clearly be applied in the context of multiple and different experimental designs. In FTD, this was the case of a couple of studies that analysed common variants in cohorts characterised by a genetic signature carried in two FTD genes – *GRN* and *C9orf72* – to specifically look for disease modifiers (i.e. genetic factors which influence measurable variables such as age at onset or disease progression). Both studies were published in 2018: (i) one by Pottier et al. assessing a cohort of 592 patients (382 discovery phase; 210 replication phase) carrying Mendelian mutations in *GRN* (and some being pathologically defined as FTLD-TDPs without *GRN* mutations) that led to the replication of the above-described locus on chromosome 7p21 and the identification of a new locus on chromosome 8p21.3 [62] and (ii) one by Zhang et al. assessing a cohort of 331 (144 discovery phase; 187 replication phase) *C9orf72* expansion carriers that suggested a locus on chromosome 6 acting as a modifier for age at onset [63]. Of note, a previous study by Barbier et al. conducted on a cohort of 504 patients belonging to 133 families with pathogenic mutations in both *GRN* and *C9orf72* indicated potential chromosome X-linked modifiers of age at onset (for *C9orf72* expansions carriers but not for *GRN* mutation carriers) [64]. More recently, a GWAS on 636 FTLD-TDP pathologically confirmed cases (517 discovery phase; 119 replication phase) – and not carrying mutations in any of the known FTD genes – by Pottier et al. suggested three risk loci on chromosomes 7q36, 19p13.11 and 6p21.32 [56]. Of note, provided there being different pathological subtypes within the FTLD-TDP spectrum (i.e. subtypes 'A', 'B', 'C' and 'D'; c.f [65]), this study suggested that (i) although the 7q36 locus had been previously associated with idiopathic ALS, here the signal represented an independent association; (ii) the association with the 19p13.11 locus appeared to be the same as previously indicated in ALS studies, and it was specific to the FTLD-TDP subtype 'B'; and (iii) the rare T-allele of rs5848, located within *GRN*'s 3'-UTR, appeared to specifically (and exclusively) increase risk for cases belonging to the FTLD-TDP subtype 'A' [56].

GWAS results described in this section are summarised in Table 1.

Although one might gather from these sections that the FTD genetics arena is globally quite heterogeneous, there are reasons to suspect that homogeneous subpopulations of patients exist and can be better defined and predicted through tailored genetic (and bioinformatics) studies [21, 22].

Missing Heritability

Despite heterogeneity, it might be argued that FTD is a disorder with a robust hereditary component. However, our genetic understanding of FTD is still considerably incomplete in sporadic as well as in familial FTD (e.g. there are families where Mendelian mutations have not been isolated) [4]. It follows that missing heritability is a critical unresolved issue in FTD [66].

Recently, a number of sequencing projects in FTLD-TDP, clinical FTD and FTD-ALS cases further characterised mutations in either already established Mendelian or what could be considered as 'novel' FTD genes. For example, an excess of loss-of-function variants in FTLD-TDP cases was evident in a number of genes (i.e. *DHX58*, *IRF3*, *IRF7*, *IRF8*, *NOD2* and *TRIM21*) suggested to be in strong functional link with *TBK1* within inflammatory response pathways [56]. Further, mutations were described in *SORT1* and in a Belgian FTD cohort and subsequently confirmed in Mediterranean FTD cases [67]; *CCNF* in FTD and ALS cases [68]; *TREM2*, *CSF1R* and *AARS2* in Asian FTD cases [69, 70]; and *TYROBP* in Italian FTD-ALS pedigrees [71]. Besides many of these mutations needing addi-

Table 1 Summary of GWAS studies in FTD

FTD cohort	Total cases	Locus	markers	p-values (joint)	Affected gene	Biological meaning	Year	Reference
FTLD-TDP	604	chr 7p21	rs1020004 rs6966915 rs1990622	5.00×10^{-11} 1.63×10^{-11} 1.08×10^{-11}	*TMEM106B*	Increased expression of *TMEM106B*; endolysosomes	2010	59
Clinical FTD	2,154	chr 6p21.3	rs1980493 rs9268856 rs9268877	1.57×10^{-8} 5.51×10^{-9} 1.05×10^{-8}	*BTNL2* *HLA-DRA / DRB*	Changes in methylation pattern at *HLA-DRA*; immune response	2014	60
Clinical bvFTD	1,377	chr 11q14	rs302668	2.44×10^{-7}	*RAB38*	Decreased expression of *RAB38*		
Italian FTD	530	chr 2p16.3	rs17042852	2.01×10^{-7}	NA	NA	2015	61
		chr 17q25.3	rs906175	1.22×10^{-7}	*RFNG*; *AATK*; *MIR1250*	Decreased expression of *RFNG*, *AATK*, *MIR1250*; neurogenesis; neuronal apoptosis; regulation of gene expression		
GRN mutations / *C9orf72* expansion carriers	504	chr X-linked modifiers	NA	NA	NA	Effect on AAO* in *C9orf72* expansion carriers	2017	64
GRN mutations carriers	592	chr 7p21	rs1990622	3.54×10^{-16}	*TMEM106B*	Increased expression of *TMEM106B*; endolysosomes	2018	62
		chr 8p21.3	rs36196656	1.58×10^{-6}	*GFRA2*	Decreased expression of *GFRA2*; GDNF signalling pathway		
C9orf72 expansion carriers	331	chr 6	rs9357140	1.0×10^{-6}	NA	Changes in methylation pattern; effect on AAO*; increased expression of *HLA-DRB1*; immune response	2018	63
FTLD-TDP	636	chr 7q36	rs118113626	4.8×10^{-8}	*DPP6*	NA	2019	56
		chr 19p13.11	rs1297319	1.27×10^{-8}	*UNC13A*	FTD-TDP subtype 'B' signature		
		chr 6p21.32	rs17219281	3.22×10^{-8}	*HLA-DQA2 / -DQB2*	Increased expression of *HLA-DQA2 / -DQB2*		

* AAO: age at onset

tional replication, the above studies further support the notion of population and syndrome heterogeneity characterising genetics of FTD.

Considering sFTD, the scenario is possibly even more complicated. A first issue is that GWAS in FTD have still been quite underpowered to date. This can, e.g. be appreciated by comparing numbers of cases studied across different neurodegenerative diseases such as AD (n ~ 90,000 [72]) and PD (n ~ 40,000 [73]) vs. the largest FTD-GWAS so far (n ~ 3500 [60]). A second issue is represented by the fact that underpowered GWAS in FTD have hampered appreciating the global contribution of the multiple risk markers with small effect size through, e.g. polygenic risk scoring (PRS). PRS would indeed serve the purpose of measuring how well the global genetic architecture of risk discriminates sFTD cases from controls (and/or other closely related neurodegenerations). PRS aggregates whole-genome genetic risk into a single score using a test sample to weight SNP contribution to a trait and assesses such weights in an independent target sample [74]. Since PRS has never been done in FTD, the actual genetic architecture that confers globally increased risk for developing sFTD remains elusive, even more so when considering the different FTD subtypes: (i) the clinical syndromes belonging to the core FTD spectrum, i.e. the behavioural and language variants [18, 20], and (ii) the pathologically defined subtypes characterised by Tau and TDP-43 (FTLD-tau, FTLD-TDP) or p62 (FTLD-UPS [ubiquitin proteasome]) or FUS, EWS and TAF15 (collectively referred to as FTLD-FET) protein aggregates [54, 65].

Although a large GWAS meta-analysis for sFTD is currently (at the time this chapter is being written) ongoing within the IFGC program – including over 5000 cases – it is clear that the genetic architecture underpinning sFTD (and its various subtypes) is still poorly defined and understood; thus, more work in this area is warranted.

From Genetics to Disease Biology

Despite our poor understanding of environmental risk factor in FTD and the work ahead in further characterising the genetic architecture of risk, there is an important issue we can start addressing now: translation of our current knowledge of FTD's genetics into functional understanding of disease. This is indeed among the major topics gaining momentum in the biomedical field focusing on complex neurodegenerative disorders (including FTD) [75].

Translating GWAS Genetics into Biological Meaning

One of the biggest challenges in population genetics is the interpretation of the risk signals derived from GWAS. Whilst GWAS are instrumental in discriminating genetic risk markers and loci that associate with a trait of interest, such signals are not directly informative on the impacted gene(s) or disease mechanism(s) [76]. SNPs highlighted by GWAS are for the very vast majority non-coding (intronic or intergenic) meaning that additional investigations are required to identify the actual gene(s) and pathway(s) targeted by the risk variants within the risk locus [3, 77]. This is not a trivial issue since the understanding of impacted genes and pathways is of primary importance to untangle the functional role of the risk variants and generate more accurate disease models.

Besides increasing the resolution in prioritising genes at GWAS loci, e.g. through ad-hoc gene-burden analyses [78], other strategies involving integration of genetic and other types of data – e.g. gene expression, protein-protein interaction and pathway analyses – are being fine-tuned [76]. Indeed, a first point to clarify is whether any SNP highlighted by a GWAS exerts an effect on gene expression: this is done by assessing expression quantitative trait loci (eQTL) [79], a bioinformatics technique that evaluates expression levels (mRNA) of genes in *cis* with the risk allele(s) of the associated SNPs within the locus of interest. When the risk allele significantly associates with a change of expression of a *cis*-gene, the latter might be bona fide considered the biological target of the genetic variant. There are other types of QTL analyses, e.g. methylation (mQTL), splicing (sQTL) and protein (pQTL) [80], that focus on the identification of alterations in methylation profile, splicing or protein levels. Such quantitative traits might be used as proxies to prioritise genes and support the definition of molecular mechanisms modulated by GWAS SNPs. And, clearly, these will need to be further validated in functional assays to confirm they are truly associated with a possible disease mechanism.

The FTLD-TDP GWAS, showing association with SNPs at the locus on chromosome 7p21 [59], revealed the risk alleles to affect expression levels (increased) of the *cis*-gene *TMEM106B* [59]. Further analyses showed elevated basal levels of *TMEM106B* in FTLD brains affected by TDP-43 pathology [81]. Also, multiple follow-up studies confirmed *TMEM106B* to be functionally relevant for FTD hinting at an interplay with two known fFTD (Mendelian) genes, i.e. *GRN* and *CHMP2B*. Studies on TMEM106B protein suggested its involvement in the endolysosomal system together with CHMP2B [82]. Furthermore, overexpression of *TMEM106B* was shown to be associated with impairment of the endolysosomal system and an increase in the levels of GRN [81], whilst ablation/reduction of *TMEM106B* was able to rescue the endolysosomal phenotype observed in *Grn*-deficient mice [83] or in *CHMP2B* mutants [84]. The GWAS on *GRN* mutation carriers [62] supported the notion that *TMEM106B* is a modifier in *GRN* mutation carriers (in line with the original study [59]) and, additionally, suggested the risk allele of the top SNP at the chromosome 8p21.3 locus being a *cis*-eQTL of the GDNF family receptor alpha 2 (*GFRA2*) gene. The GFRA2 protein was shown to co-precipitate with the GRN protein possibly inferring to a potential involvement of the GDNF signalling pathway (a pathway promoting survival of neurons) in *GRN* mutation carriers. The clinical FTD-GWAS [60] indicated that both an mQTL for *HLA-DRA* (6p21.3 locus) and an eQTL for *RAB38* (11q14 locus) appeared to explain how the biological effect at those loci was possibly mediated. mQTLs at the *HLA* locus were also suggested in Zhang et al. where regulation of expression in brain cortex of pro-inflammatory elements seemed to influence age at onset in FTD patients [63]. Further support for the involvement of the immune system in FTLD-TDP pathogenesis was more recently provided by Pottier et al. who showed (i) eQTLs driven by the risk allele of the top SNP at the chromosome 6p21.32 locus leading to increased expression of *HLA-DQA2* and *HLA-DQB2* in the brain and (ii) excess of genetic burden in a number of genes acting in epistasis with *TBK1* within innate immune signalling pathways [56].

The locus characterisation described in the above paragraph are summarised in Fig. 1.

Clearly, several of the above studies strongly suggest that perturbation of multiple genes and pathways of the immune system might specifically underpin subpopulations of patients and contribute to FTD pathogenesis. This view appears to be further supported by a handful of earlier studies hinting at altered cytokine profiling in the cerebrospinal fluid (CSF) and/or serum of FTD patients [85, 86] and the identification of changes in the expression of FTD-immune pleiotropic genes (within the *HLA* region) in post-mortem brain tissue of FTD patients with an enriched microglia/macrophage signature [87].

Are Mendelian and Sporadic FTD the Same Disorder?

A relevant point in FTD research is that Mendelian genes are instrumental for disease modelling, i.e. they can be studied in in vitro/in vivo model systems (e.g. transgenic cellular and animal models or patient-derived iPS cells) to gather insights into the molecular mechanisms of disease. This is fundamental to understand the cellular functions that are compromised during disease onset and progression and to identify potential targets for therapeutic intervention.

This approach is hardly applicable to sporadic disease. Sporadic cases are associated with multiple risk factors that are very difficult to model

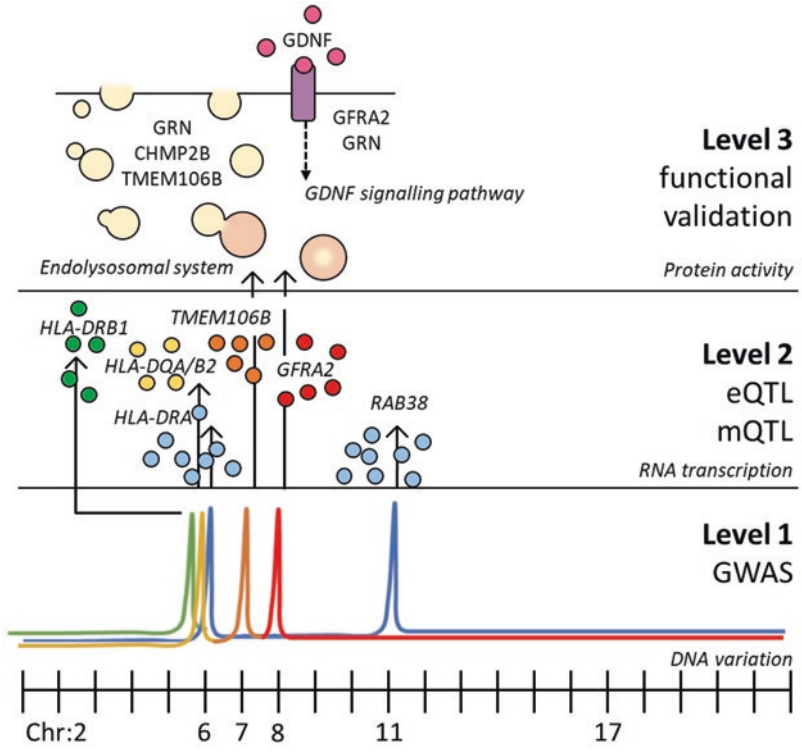

Fig. 1 Translating (sporadic) genetics into functional meaning. The pipeline for translating GWAS genetic signals into biological functions is illustrated. A GWAS is conducted to isolate 'DNA level information' on risk variants associated with FTD (*level 1*). The risk variants at the risk locus are assessed for effect(s) on gene transcription levels and/or methylation patterns (*level 2*). Validation at the protein level is pursued through functional models to characterise the impacted pathway(s) and the associated molecular mechanisms of disease (*level 3*). The original FTLD-TDP GWAS signals are depicted in orange, the International FTLD-TDP GWAS signals are depicted in red, the GRN-GWAS signals are depicted in yellow, the methylation GWAS on *C9orf72* expansion carrier signals are depicted in green and the clinical FTD-GWAS signals are depicted in blue

because they (i) feature small effect size, (ii) act as a whole (thus, the experimental system would need to model multiple risk factors at the same time) and (iii) are non-coding (thus, it is for the most unclear which gene/protein they impact). On top, the contribution of environmental exposures is, to date, impossible to model [77].

Familial models of disease do not fully capture or reflect disease complexity. In fact, by almost exclusively focusing on fFTD, FTD models are currently limited (despite a number of studies on *TMEM106B* [22, 88]) to models focused on Mendelian genes (*MAPT*, *GRN*, *C9orf72*) or models of tau pathology, a feature that is seen in FTLD-tau and beyond (e.g. AD but also progressive supranuclear palsy [PSP] or CBD). As a consequence, using the familial models as proxies for the entire disease spectrum (only because models for the sporadic forms of disease are not available) might not be entirely successful. Such *modus operandi* indirectly relies on the assumption that, since familial and sporadic FTD are clinically classified under the 'same label', the molecular mechanisms and pathways altered in familial cases might be the same or similar to those in the sporadic ones. This is, however, still an open and unexplored question. One possible example of shared mechanisms comes from the *MAPT* locus. In FTLD-tau, *MAPT* mutations (i.e. coding variants in exons 1, 9–13 [89, 90]) or heterogeneous genetic variability (e.g. intronic variants affecting expression and/or splicing of exon 10 [91, 92] or structural variants [93, 94]) cause disease and lead to tau pathology. At the same time, when considering the ~900 kb H1/H2 haplotype inversion at the *MAPT* locus [95], a yet to be identified combination of markers on this stretch may increase disease risk in a subgroup of patients with parkinsonism or broad FTD-like dementia phenotypes [96]. Further studying the genetics at the basis of tau pathology might help shedding light on communal disease mechanisms across fFTDs and sFTDs, as well as FTD and other tauopathies.

Moreover, one must not forget about a number of critical issues associated with the study of familial and/or pathologically defined cohorts: (i) they represent a minority of all FTD cases, (ii) they might be underpowered, (iii) they might provide little or inadequate information on disease mechanism(s) underpinning the various clinical syndromes and (iv) drugs and intervention measures, currently under preclinical and clinical investigation (trials), appear tailored to fFTD or FTLD-tau only [97].

There is therefore an urgent need to expand the focus to sporadic FTD and assess disease pathways that might be communal across fFTDs and sFTDs, knowledge that will be critical and instrumental to pave the way for developing clinical trials and means for therapeutic intervention addressing all FTD cases.

Risk Pathway In Silico Modelling

Multiple genes and genetic risk variants associate with FTD. However, as in the case of other complex neurodegenerations such as PD and AD, it is difficult to portrait why and how so many different genetic elements lead to the 'same disease'.

It is well known that functional research is still not well equipped to model multiple genetic players at the same time. The classical approach relies on studying single genes (and risk factors) in isolation, collating reductionist pieces of information to recreate a global picture of disease. However, whilst this approach has been successful, e.g. the amyloid cascade hypothesis in AD based on functional work assessing mutations in *APP* and *PSEN*s [98], it appears promising, e.g. ongoing studies focusing on tau pathology [99] and the biology of *GRN*, *C9orf72* and *TMEM106B* [21, 22], only in a limited number of cases due to intense and costly mechanistic studies that impact the timely dissection of disease mechanisms [100].

Conversely, more recent bioinformatics and systems biology methods – incorporating notions from graph theory, network analysis and machine learning – have seen the light to model the genetic landscape associated with a complex trait and predict risk pathways to assist hypothesis-driven functional validation in the wet lab. This represents a holistic paradigm shift where risk pathway(s) are hypothesised, in silico, a priori, in a time- and cost-effective fashion, and can be

subsequently tested. Systems biology approaches based on network analysis have started being applied to FTD to evaluate possible functional commonalities across FTD genes.

Weighted gene co-expression network analysis (WGCNA) – a bioinformatics method that applies mathematics, statistics and graph theory to expression (and possibly tissue-specific) level data [101] – was applied to evaluate impacted biological processes/pathways and connectivity of genes of interest within co-expression networks in knowingly impacted brain regions [102]. Specifically, FTD-relevant genes (called 'seeds' in this context) were mapped to modules representative of expression profiles in the brain and mathematically assessed for their relevance within each module, prior functionally annotating each module. Such a pipeline allows to swiftly investigate the set of functions in which each single FTD genes might be expected to be involved. At the same time, it allows to evaluate possible functional overlap(s) across several different genes in a brain regional-specific manner. The FTD-WGCNA work [102] did reduce the impacted biological processes/pathways (for both familial and sporadic forms of disease) down to (i) gene expression, DNA protection (e.g. DNA damage repair) and protein metabolism (e.g. waste disposal) processes for a majority of FTD-Mendelian genes and (ii) immune response and endolysosomal metabolism for sFTD risk factors. The intrinsic novelties of this approach can be summarised as follows: (i) the annotated modules are critical in mapping specific impacted biological processes to specific brain regions relevant to disease, and (ii) the list of genes found to be co-expressed with the FTD-relevant genes might provide informative suggestions on novel potential genetic and/or functional candidates. For example, *TBK1* mapped to a co-expression module together with *C9orf72*, *VCP*, *UBQLN2* and *OPTN* [102]. The fact that mutations in *TBK1* were isolated in the FTD and FTD-ALS spectrum reinforces the notion that members of modules including FTD-relevant genes might be (retrospectively) considered for prioritising sequencing and burden analyses aimed at the discovery of novel genes associated with disease.

Weighted protein-protein interaction network analysis (WPPINA) – another bioinformatics approach, this time taking into account protein-protein interactions (PPI) – was applied to extract physical interactors of the protein products of FTD-relevant genes [103]. This method first determined (two-layered) protein interactomes around each FTD-relevant gene (or 'seed') and then investigated communal nodes (interactors) across as many seeds as possible. Such interconnectome (made of so-called inter-interactome hubs [IIH]) was then used to perform functional annotation analysis (similarly to the case of the WGCNA modules). The FTD-WPPINA work [103] confirmed three major biological processes/pathways shared across FTD-relevant genes (previously also suggested by the FTD-WGCNA) such as gene expression, DNA damage response and waste disposal. Similarly (although slightly differently) to the WGCNA approach described above, WPPINA was instrumental in indicating, in addition to the above highlighted impacted pathways, a list of potential genetic and/or functional candidates either directly or indirectly interacting with the protein products of FTD-relevant genes. This is all the more important in that it provides protein targets within impacted pathways to be taken forwards for (i) designing ad hoc functional assays to model disease and (ii) lead to the identification of potential drug targets. Moreover, WPPINA proved promising in other contexts such as those of prioritising genes within GWAS loci and comparing/discriminating impacted biological processes across neurodegenerative diseases. Specifically, WPPINA was helpful in narrowing down potential functional candidates at PD-GWAS loci and proved useful in computationally discriminating specific subcellular pathways whilst comparing FTD and PD [104]. WPPINA suggested that, for same (or similar) impacted biological processes (e.g. biology of 'stress' and 'waste disposal'), it was 'endoplasmic reticulum (ER) stressors' that correlated with FTD vs. 'mitochondria stressors' in PD or elements of the 'unfolded protein response' and 'ubiquitin proteasome' in FTD vs. 'autophagy' and 'lysosomal' biology in PD [104].

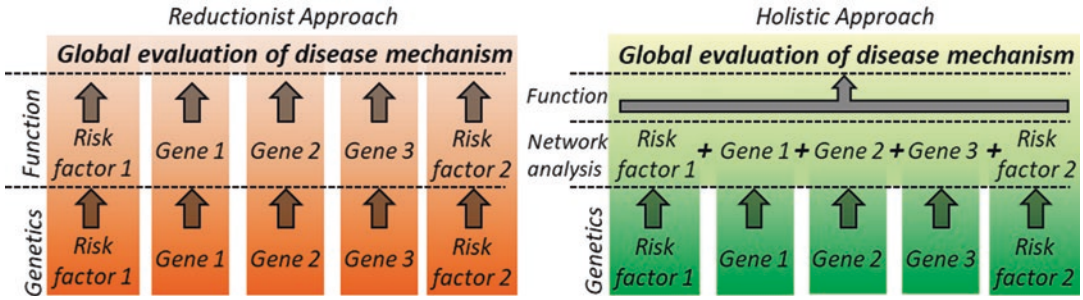

Fig. 2 Reductionist and holistic approach scheme. The 'reductionist' approach studies one gene/risk marker at a time. The 'holistic' approach aims at defining communal functional features across the multiple gene(s)/risk marker(s). Both approaches are important. They are not mutually exclusive but rather incremental and complementary

It is relevant to note that, in parallel with the WGCNA and WPPINA studies and in the context of bridging the biology of fFTDs and sFTDs, additional bioinformatics work showed association of risk variants in sporadic FTD-GWAS with the biology of immune-related disorders [87] or RNA metabolism and cell death pathways to be associated with FTD's language variant syndrome [105] and cell cycle and immune signalling to be associated with tissue-specific expression changes in bvFTD [106].

It must be acknowledged that these are in silico approaches and no practical steps have yet been undertaken to functionally prove the above highlighted risk pathways. Nevertheless, discussions between field professionals (e.g. geneticists, bioinformaticians and functional biologists) on these topics have started and are ongoing, with a focus on FTD models as well. Functional studies will be the next critical step in comparing and understanding disease processes affected in fFTD and sFTD and may subsequently support the development of interventional measures.

Future Directions

The study of FTD – from genetic dissection to disease modelling – will require a significant number of efforts in the years to come. Importantly, the research carried out this far provides us with a solid basis to optimistically look into the future with a clear understanding of the (still) open challenges that will need to be addressed.

FTD genetics will require more powerful and in-depth studies – based on GWAS, fine-mapping and sequencing techniques – to (i) dissect common (i.e. prioritise genes impacted by the genetic risk markers isolated through GWAS), oligogenic and rare genetic factors underpinning disease; (ii) tackle missing heritability; (iii) define the genetic architecture of sFTD with particular focus on the different FTD subtypes (based on both clinical and pathological diagnoses); and (iv) foster meta- and pleiotropy analyses with other closely related neurodegenerative conditions.

In parallel, it will be critical to translate the genetic findings into model systems and molecular mechanisms of disease. More specifically, it will be necessary to implement a paradigm shift from reductionist to holistic approaches to interpret genetics (Fig. 2) and subsequently assist and drive functional studies. This means that precise experimental models (including cell-specificity studies) investigating and validating risk pathways and biological processes that are impacted by genetic variability will (have to) become reality [107, 108].

All this taken together will be instrumental in improving our understanding of the aetiopathogenesis of disease, help stratifying patients for syndrome-specific clinical trials, highlighting efficient endpoints for disease monitoring and therapeutic intervention and deciphering whether and to what extent molecular mechanisms at the basis of fFTD and sFTD are overlapping, convergent or divergent.

Normalising these strategies will be extremely valuable in setting the ground for the development of effective disease management measures in FTD within the frame of precision medicine.

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FTLD Treatment: Current Practice and Future Possibilities

Peter A. Ljubenkov and Adam L. Boxer

Non-pharmacological Management in FTD

Early Education

Many patients and caregivers are unfamiliar with behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) when these diagnoses are first discussed in clinic. For this reason, early therapeutic invention often involves basic education about the disease. The Association for Frontotemporal Degeneration (AFTD) is a useful reference for patients in North America (www.theaftd.org) and Australia (www.theaftd.org.au), and Rare Dementia Support (www.raredementiasupport.org) offers similar resources in the United Kingdom. These organizations provide basic high-quality information about diagnoses, research opportunities (including clinical trials), and support group services. Patients who are particularly interested in research may also be referred to a local academic center belonging to a large multisite research consortium, such as the Genetic Frontotemporal Dementia Initiative (GENFI, genfi.org.uk) in the United Kingdom and Europe and the ALLFTD research consortium in the United States (www.allftd.org). Consortia of this kind often provide the best infrastructure to identify and counsel familial FTD cohorts and navigate patients toward relevant clinical trials of interest. Alternatively, patients who carry a strong family history of neurodegenerative disease but who are not interested in research may benefit from an early referral to an independent genetic counselor, particularly when Mendelian forms of FTD are expected.

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Initial Safety Evaluations

In bvFTD, like many dementia syndromes, it is important to assess a patient's current level of safety during their early and subsequent evaluations [1]. Patients with features of the behavioral variant of frontotemporal dementia (bvFTD) [2] in particular often lack the capacity to avoid danger, due to disinhibition, apathy, and poor understanding of the internal state of others. Moreover, while patients with bvFTD may occasionally exhibit violent behaviors, they are also at risk of physical or financial victimization due to their impairments in social cognition. Table 1 details a brief list of potential safety concerns and viable intervention strategies in patients with bvFTD. Of these concerns, driving safety is often an early and contentious point of discussion. While a physician's responsibilities may differ by country

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Table 1 Common safety concerns in patients with FTD

Safety concern	Recommended intervention
Firearm and other weapons	Remove all weapons from the home Secure weapons in a locked safe the patient can't access
Driving safety	Report patient to their jurisdictions' relevant authority that controls driving privileges Consider hiding vehicle keys or disabling vehicles if necessary
Medication mismanagement	Recommend caregiver take over medication management Consider securing medication in a locked box or cabinet that the patient can't access Review medication list to limit unnecessary polypharmacy
Poor self-care	Provide early education to caregiver regarding loss of independence in hygiene
Injury using kitchen appliances	Discourage independent access to dangerous kitchen appliances such as the stove or the oven Consider disabling or removing dangerous appliances if the patient must be left unattended
Wandering	Provide early education to caregivers about the need for increased supervision and additional caregiver support Consider ID bracelets, smartphone tracking apps, and/or tracking key fobs Consider door alarms and door locks requiring a key Coordinate with local law enforcement to prepare for potential wandering events
Financial risk/ scams	Consider establishing a durable power of attorney (DPOA) for financial decisions as soon as possible Consider limiting a patient's independent access to bank accounts or credit cards Report any concerns for financial abuse to the local jurisdiction's equivalent of adult protective services
Undue approach of strangers	Encourage direct supervision in public places Consider limiting exposure to crowded public places if behaviors are hard to control Consider education of members of the patient's immediate community to promote acceptance and minimize misunderstanding Report any concerns for financial abuse to the local jurisdiction's equivalent of adult protective services
Falls	Educate patient and caregiver about impulsivity if it is present Remove clutter and tripping hazards from walkways and stairs Improve lighting and color contrast on steps Move high-use items to mid-level cabinets that don't require stretching or bending Consider increasing placement of handrails in the home (especially in the shower and by the toilet) Ensure adequate assistance to and from the restroom, particularly at night Consider installing night-lights and a bedside commode If significant parkinsonism is present, consider a weighted walker that defaults to a locked position (such as the U-step)

and jurisdiction, a patient's driving privileges should be reevaluated in the face of caregiver concern, a recent car accident, a recent traffic citation, a recent volitional restriction of the scope of driving, concern for impulsive or aggressive behavior, or any cognitive testing supporting a diagnosis of dementia [3]. Home firearms are also among the most urgent safety concerns in bvFTD and must be removed or secured as soon as a dementia diagnosis is made. Ultimately, if a patient presents persistent safety concerns to themselves or others, a higher level of care may need consideration.

Behavioral Interventions

Caregiver burden is increased in bvFTD relative to Alzheimer's disease dementia [4], due in part to the increase in a variety of difficult and disruptive behaviors. Apathy, disinhibition, compulsive

behaviors, loss of empathy, and dietary changes make up the core clinical features of the bvFTD [2]. These behavioral features are also commonly found in a variety of conditions within the greater clinical spectrum correlating with FTLD pathology on autopsy, especially in advanced stages of disease. In particular, disabling behavioral changes are a well-described phenomenon in FTD with motor neuron disease (FTD-MND) [5], semantic variant primary progressive aphasia (svPPA) [6], non-fluent agrammatic variant primary progressive aphasia (nfvPPA) [7], progressive supranuclear palsy (PSP) [8], and cortical basal syndrome (CBS) [9]. Unfortunately, pharmacotherapy often provides little efficacy in curbing difficult behaviors. For this reason, the core of behavioral management in bvFTD involves caregiver strategies for behavioral redirection and environmental modification. While few studies have sought to test the efficacy of these behavioral interventions in patients with dementia, one potentially viable consensus framework for behavioral intervention was established by Kale et al. in 2014 [10]. This proposed "DICE" model of behavioral intervention advocates careful *d*escription of the circumstances of problem behaviors, thorough *i*nvestigation of potential inciting/contributing factors, *c*reation of an action plan to alleviate exacerbating factors, and follow-up *e*valuation to address the need for implementation of additional interventions. The DICE model advocates three avenues of investigation when considering preventable causes of unwanted behavior: the patient, the caregiver, and the environment. Potentially augmentable patient factors include untreated medical comorbidity (leading to discomfort or delirium), untreated psychiatric comorbidity (including depression and anxiety), untreated pain, untreated sensory deficits, boredom, fear, and poor sleep hygiene. Preventable caregiver factors include a limited understanding of a patient's dementia syndrome, inappropriate expectations for a patient with dementia, a confrontational communication style, and an overly nuanced communication style. Potentially harmful environmental features include unpredictability in the daily routine, a chaotic or uncomfortable physical environment, a poorly lit environment, an overabundance of distractions or choices, or a lack of recreational distractions. The authors of the DICE model also encourage assessment of safety risk, and while dangerous behaviors require immediate intervention, non-harmful repetitive behaviors may be best managed with acceptance and reframing of expectations.

Speech Therapy

In patients with features of primary progressive aphasia (PPA) [11], treatment typically focuses on referral to a licensed speech and language pathologist (SLP). While clinical trial data is limited, an experienced SLP may offer a variety of interventions and compensatory strategies to patients with PPA. As discussed in a recent review by Volkmer et al. in 2019 [12], PPA interventions commonly tap strategies training individual word retrieval, trained scripts, and compensatory communication methods. A systematic review of 39 studies suggests that word retrieval interventions (e.g., repetitively reading specific words with associated pictures) may transiently help patients with PPA retrieve specific trained words, though these gains may not always be maintained or generalized [13]. Additionally, non-randomized trials in nfvPPA suggest that script training, a common therapy in stroke aphasia, may improve the intelligibility of trained and untrained topics, and these gains may persist for up to a year after treatment [14, 15]. Compensatory communication strategies include communication skills training, including greater implementation of nonverbal gestures, and augmentative and alternative communication (AAC) devices in the form or communication cards, phone apps, or tablet-based devices [12].

Additional Non-pharmacological Interventions

There is some epidemiological data supporting a healthy diet, increased physical activity, increased cognitive engagement, and increased social engagement as mechanisms to prevent all causes of

dementia [16]. Many of these lifestyle features are usually hypothesized to modify the risk for vascular dementia rather than the pathophysiology of FTLD. There is, however, relatively new evidence that cognitive activity (e.g., reading or spending time with friends) and physical exercise may be associated with slower rates of clinical decline in familial forms of frontotemporal dementia [17]. While the direction of causality is hard to establish in this early data, increased social engagement and physical exercises tend to be fundamentally positive for quality of life and thus represent low-risk strategies for treatment and prevention of FTD.

Current Pharmacotherapy in FTD

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) remain the central focus of current pharmacotherapy targeting the behavioral features FTD [18], despite scarce randomized clinical trial support. This practice is supported by early evidence linking disruptive behaviors, such as agitation and aggression, to deficits in serotonergic signaling [19]. Additionally, SSRIs have long been known to induce hyposexuality, which may be a desired side effect in patients with bvFTD [20]. PET studies reflect reduced 5-HT_{1A} receptors throughout multiple frontotemporal regions [21] in bvFTD. Furthermore, postmortem studies in autopsy-confirmed FTLD further support a wide spread of largely postsynaptic deficits involving reduction of 5-HT_1 and $5HT_{2A}$ receptors throughout multiple frontal and temporal cortical regions [22–24], as well as 40% loss of serotoninergic neurons in the median raphe nucleus [25]. Consistent with these early pathologic studies, early open-label SSRI studies in FTD suggested benefits in the treatment of depressive symptoms and a variety of core bvFTD features, including disinhibition, compulsions, and dietary changes [26]. Early case data on paroxetine, for instance, suggested benefits in curbing depressive and obsessive symptoms in FTD [20], and in a 14-month open-label trial of paroxetine (20 mg daily), patients experienced improvement of repetitive behaviors and overall neuropsychiatric index (NPI) score [27]. However, 40 mg daily dosing of paroxetine failed to improve behavior in a follow-up randomized crossover study enrolling ten patients with FTD (and, in fact, patients on active drug performed nonsignificantly worse on cognitive testing [28]). This failure may have been due to the off-target anticholinergic effects of paroxetine. On this note, there is case evidence that anticholinergic tricyclic antidepressants such as clomipramine may also be poorly tolerated in semantic dementia [20]. Current pharmacotherapy trends in bvFTD tend to make greater use of SSRIs with fewer off-target effects, such as citalopram, escitalopram, and sertraline, though trial data is limited in these drugs. Sertraline has so far been shown to improve behaviors in small open-label trials in bvFTD and svPPA [29]. Additionally, a 6-week open-label trial of citalopram (titrated to 40 mg daily) was associated with improvements in depression, disinhibition, and irritability in 15 patients with FTD [30]. Trazodone (a weak SSRI and 5-HT1A, 5-HT1C, and 5-HT2 antagonist) [31] has perhaps the best supported therapeutic rationale in bvFTD, as it yielded significant improvements in depressive symptoms, irritability, agitation, and dietary changes in a randomized, double-blind, placebo-controlled crossover study in ten patients [32]. However, at the dose used in this trial (150 mg daily), patients experienced treatment emergent effects of fatigue, dizziness, hypotension, and cold extremities. Given these and other known side effects of trazodone, it has failed to supplant more typical SSRIs in the standard care of FTD. Additionally, aside from SSRIs, there is a lack of published information supporting or discouraging the use of other depression or anxiety pharmacotherapy in FTD (though there is limited case data supporting the use of mirtazapine for sleep [20] and discouraging the use of buspirone in nvPPA [20]).

Antipsychotics in FTLD

Antipsychotics are commonly used off-label to manage FTD behavioral features, despite a rela-

tive paucity of trial data and the high risks associated with these medications. While CSF characterization suggests elevations in dopamine signaling may be associated with increase agitation and aggression in FTD [19], PET studies have revealed overall deficits in dopaminergic receptor binding in striatal [33] and frontal cortical regions [34] in FTD. It is therefore not surprising that patients with FTD may be more susceptible to the extrapyramidal side effects of antipsychotic medications [35]. Additionally, antipsychotics carry a black box warning from the US Food and Drug Administration (FDA) for increased risk of mortality. Moreover, the increased mortality risks of antipsychotics may persist for more than a year after cessation of use [36]. In light of their inherent risks, antipsychotics are used with significant caution in FTD, often as a last resort under a palliative rationale.

Among the atypical antipsychotics, low-dose quetiapine is most often used in bvFTD, given its relatively low rate of extrapyramidal symptoms (EPS) [37, 38] and potentially less severe impact on mortality [39]. So far, limited case data has suggested that quetiapine may have some benefit on agitation [20], but these findings have not been replicated in a clinical trial. Clozapine is also known for its low incidence of EPS [40], but it is seldom used in FTD due to its risk of aplastic anemia. Olanzapine was also found to be helpful in suppressing agitation in an open-label trial with 17 patients with FTD [9], but patients receiving treatment also experienced an increase in EPS [41]. Additionally, olanzapine is associated with increased metabolic syndrome and a relatively high mortality risk compared to quetiapine [39]. Aripiprazole has been used to suppress inappropriate vocalizations in at least one case report [42], but published data on this drug is otherwise limited. Additionally, risperidone has also been effective in stabilizing mood and agitation in case reports [20, 43], but this medication and haloperidol are used relatively infrequently in clinical practice due to their particularly high risk of EPS and morality, even in comparison to the mortality risks of other antipsychotics [39].

Poor Rationale for Alzheimer's Medications in FTD

Previous autopsy studies suggest a relative sparing of the cholinergic system in patients with FTLD pathology on autopsy [23, 24]. For this reason, there is not a firm biological basis for use of cholinesterase inhibitors in FTD clinical syndromes. However, due to the relative paucity of alternative treatments, cholinesterase inhibitors were previously commonly used in FTD after their approval in Alzheimer's disease [44, 45]. Additionally, early trial data appeared to modestly support the use of cholinesterase inhibitors, but these trials contained potential confounding factors that limited their value [46]. For instance, in an early trial, galantamine appeared to stabilize some symptoms in patients with PPA [47], but this modest secondary finding may have been driven by inclusion of patients with logopenic variant PPA (typically associated with Alzheimer's disease pathology). Additionally, a small open-label study of rivastigmine in bvFTD observed a trend of decreased caregiver burden and behavioral impairment after treatment [48], but these measures occasionally spontaneously improve on their own in bvFTD, as apathy overshadows other behaviors. Trials with donepezil have been more definitely discouraging. In a pilot study with 23 patients and separate small open-label trial, donepezil was associated with worsening neuropsychiatric symptoms in FTD syndromes, and this effect improved after cessation of treatment [49, 50]. Given these results, cholinesterase inhibitors are now generally avoided in FTD cohorts. The use of memantine (weak NMDA antagonist) is also generally discouraged, as it failed to improve behavior and potentially worsened cognition in patients with bvFTD and PPA in a multicenter, randomized, double-blind, placebo-controlled trial [51].

Stimulants in FTD

Stimulants are occasionally rationalized as a tool to treat apathy, but they rarely used in the management of bvFTD given fears of increased

irritability and disinhibition. There is, however, some limited information that stimulants may occasionally be used for treatment of unwanted behaviors in bvFTD. Methylphenidate (which simulates the release and suppresses the reuptake of dopamine and norepinephrine) appeared to improve withdrawal, apathy, and irritability in an isolated bvFTD case [52]. Moreover, in an eight-patient placebo-controlled crossover trial in bvFTD, a 40 mg daily dose of methylphenidate was associated with decreased risk-taking in a novel testing paradigm [53]. Additionally, dextromethorphan (20 mg daily) appeared to improve apathy and disinhibition relative to Seroquel (20 mg daily) in a small double-blind crossover study [54].

Anticonvulsants

Anticonvulsants like valproate are commonly used to suppress the behavioral features of mania in patients with bipolar disorder, but they are less commonly used in bvFTD due to their potentially unfavorable side effect profiles. Valproate in particular is often avoided due to its risk of encephalopathy [55], hepatotoxicity [56], hyperammonemia [57], parkinsonism [58], and increased mortality [39]. There is, however, some case report data suggesting that valproate may occasionally be used to suppress agitation and hypersexuality [20, 59]. Similarly, case data suggests that carbamazepine can be helpful in suppressing indiscriminate and inappropriate sexual behavior [60]. Additionally, topiramate has been helpful in suppressing compulsive eating and drinking behaviors in a number of case studies [61–64]. While benzodiazepines also occasionally provide a nonspecific tool for sedation, they are seldom used in FTD due to their risk of paradoxical agitation, oversedation, and misuse.

Parkinsonism Medications

Patients with parkinsonism due to FTLD pathology often find little relief from L-dopa. Additionally, when patients with PSP or CBS do respond to L-dopa, the response is typically modest and short-lived [65, 66]. The parkinsonism variant of PSP [8] is, however, occasionally associated with a more measurable and sustained benefit from L-dopa. For this reason, a trial of L-dopa/carbidopa is frequently attempted even in patients with parkinsonism due to suspected underlying FTLD. Direct dopamine agonists, on the other hand, are typically discouraged in patients with suspected FTLD pathology, due to the potential for dysfunctional behaviors from dopamine dysregulation syndrome [67]. Monoamine oxidase (MAO) inhibitors are also infrequently used in clinical syndromes associated with FTLD pathology, but there is limited case data suggesting that selegiline (an MAO-B inhibitor) may improve non-motor symptoms in patients [68].

Future Therapies for FTLD

Future Therapies for Primary Tauopathies

Tau is a microtubule-associated protein that is coded by the *MAPT* gene and is thought to promote microtubule stabilization and axonal transport [69]. Frontotemporal lobar degeneration with tau pathology (FTLD-tau) is characterized by the presence of abnormal tau species, including abnormally misfolded, cleaved, and post-translationally modified (often phosphorylated and acetylated) monomers, oligomers, and filamentous aggregates [70]. Tau proteins can be further subcategorized by the predominance of a subset of six tau isoforms [71], which arise from alternative splicing of mRNA from the *MAPT* gene and chiefly differ in their inclusion or exclusion of exon 10 (which codes for one of four microtubule binding domains). Inclusion of exon 10 results in tau transcripts with four repeated microtubule binding domains (4R tau), while exclusion of exon 10 results in three binding domains (3R tau).

One possible therapeutic strategy in FTLD-tau involves mitigation of toxic loss of microtubule function. TPI-287 (TPI) is a repurposed

brain-penetrant, Taxol-related molecule that stabilizes microtubules. TPI-287 was investigated in phase 1 parallel cohort trials enrolling patients with Alzheimer's disease, PSP, and CBS (NCT01966666, NCT02133846). Unfortunately, this drug was poorly tolerated in patients with Alzheimer's disease due to increased anaphylactoid reactions. Increased falls and worsening dementia symptoms were also noted in the PSP/CBD group, and TPI-287 was not pursued in follow-up trials. Additionally, davunetide (AL-108, NAP), a short peptide that was thought to promote microtubule stability, was also not found to be efficacious in a phase 2/3 double-blind placebo-controlled trial in PSP.

Abnormal tau species demonstrate the ability to propagate from neuron to neuron and may induce conformational changes in other tau proteins in a prion-like manner [72]. Given the potential prion-like behavior of tau, anti-tau immunotherapies (including passive and active immunization strategies) are now actively explored as a means to block the interneuronal spread of tau and promote clearance of abnormal tau species [70]. While the majority of anti-tau immunotherapy therapeutic programs intend to target tau in Alzheimer's disease, there is a great interest in the parallel application of these therapies in FTLD-tau clinical trials (ClinicalTrials.gov identifier NCT03068468, NCT03413319, NCT03658135, and NCT04185415). Unfortunately, the ideal epitope for an anti-tau antibody is not clear. It also not clear that the same epitopes should be targeted across differing primary tauopathies. Preclinical studies suggest a multitude of potential epitopes for therapy including monomeric tau, oligomeric tau aggregates, hyper-phosphorylated tau, misfolded forms of tau, the tau N-terminus, the proline-rich regions of tau, microtubule binding domain, and the C-terminal regions of tau [70, 73, 74] (Table 2).

So far, clinical trials in FTLD-tau and Alzheimer's disease have directed the most attention toward passive immunization strategies against N-terminal tau epitopes. This emphasis was encouraged by early preclinical work suggesting that antibodies against the N-terminus may improve cognition in transgenic mice [73], though studies in humans have suggested the most pathogenic species of tau may be truncated at the N-terminus and retain their microtubule binding domains [75]. Unfortunately, in recent clinical trials, antibodies against N-terminal tau epitopes (BIIB092 and ABBV-8E12) have definitively failed to improve the rate of PSP clinical progression in well-powered phase 2 clinical trials (NCT03068468, NCT03413319). Additionally, termination of the BIIB092 PSP trial development program also led to early termination of a parallel phase 1 "basket trial" in patients with primary tauopathies, including CBS, nfvPPA, and pathogenic *MAPT* mutations (NCT03658135). While these events were discouraging, they may have only reflected the limited utility of targeting N-terminal epitopes in FTLD-tau. Additional upcoming trials will seek to target more diverse tau epitopes. Currently, antibodies targeting the midregions of tau, JNJ-63733657 and UCB0107, are being explored in Alzheimer's disease (NCT03375697) and an upcoming phase 1 clinical trial in PSP (NCT04185415), respectively. LY3303560, which targets N-terminal tau but shows preference for tau aggregates, is also currently being explored in a phase 2 trial in Alzheimer's disease (NCT03518073). Additionally, BIIB076, which binds to monomeric and fibrillar forms of tau, is currently being investigated in a phase I clinical trial in Alzheimer's disease (NCT03056729).

Active immunization has received much less attention than passive immunization strategies in previous anti-tau trails. So far, the AADvac1 vaccine (tau peptide aa 294–305/4R coupled to keyhole limpet hemocyanin) was safe and well tolerated in a 72-week open-label trial in patients with Alzheimer's disease [76]. In light of these findings, a phase 1 trial with AADvac1 is currently underway in patients with nfvPPA (NCT03174886). An additional vaccine, ACI-35 (which contains phosphorylated S396 and S404 tau fragments), has also been investigated in a phase 1 trial in Alzheimer's disease but has yet to be investigated in follow-up trials [77].

Antisense oligonucleotides (ASOs) provide an additional promising therapeutic mechanism

Table 2 Potential therapeutics in FTLD

	Mechanism	Indication	Phase	ClinicalTrials.gov identifier	Status
Potential therapies for C9ORF72 expansion					
BIIB078	ASO	ALS-*C9ORF72*	1	NCT03626012	Ongoing
Potential therapies for GRN haploinsufficiency					
Nimodipine	Calcium channel blocker	FTLD-*GRN*	1	NCT01835665	Negative [95]
FRM-0334	HDAC inhibitor	FTLD-*GRN*	2	NCT02149160	Negative
AL001	Anti-sortilin antibody	FTLD-*GRN*	1/2	NCT03987295	Ongoing
PR006	AVV9-based gene therapy	FTLD-*GRN*			Pending
Potential therapies for FTLD-tau					
ABBV-8E12 (C2N-8E12)	Anti-tau antibody (N-terminus)	PSP	2	NCT03413319	Negative
BIIB092 (BMS-986168)	Anti-tau antibody (N-terminus)	PSP	2	NCT03068468	Negative
		CBD, nfvPPA, TES, *MAPT*	1	NCT03658135	Terminated
LY3303560	Anti-tau antibody (N-terminus)	AD	2	NCT03518073	Active
RO 7105705 (RG 6100)	Anti-tau antibody (N-terminus)	AD	2	NCT03289143	Active
UCB0107	Anti-tau antibody (mid-domain)	PSP	1	NCT04185415	Active
JNJ-63733657	Anti-tau antibody (mid-domain)	AD	1	NCT03375697	Unavailable
BIIB076	Anti-tau antibody (monomer and filament)	AD	1	NCT03056729	Active
AADvac1	Tau vaccine	nfvPPA	1	NCT03174886	Active
ACI-35	Tau vaccine	AD	1		Unavailable
Davunetide	Microtubule stabilizations	PSP	2/3	NCT01110720	Negative [101]
TPI-287	Microtubule stabilizations	AD, PSP, CBD	I	NCT01966666, NCT02133846	Negative [102]
ASN001	o-GlcNACase inhibitor	–	1	–	–
Salsalate	Tau acetylation inhibition	PSP	1	NCT02422485	Negative
TRx0237 (LMTx)	Tau aggregation inhibition	bvFTD	3	NCT03446001	Negative
AZP2006	Tau aggregation inhibition	PSP	2	NCT04008355	Active
Lithium Carbonate	Glycogen synthase kinase inhibitor	bvFTD	2	NCT02862210	
Tideglusib	Glycogen synthase kinase inhibitor	PSP	2	NCT01049399	Negative [84]
Young plasma transfusions	Alter peripheral cell signaling	PSP	1	NCT02460731	Negative
Symptomatic FTLD treatments					
Oxytocin	Augmenting social apathy	FTD	2	NCT 01386333	Active
Rivastigmine	Cholinesterase inhibition	PSP	3	NCT02839642	Unknown

(continued)

	Mechanism	Indication	Phase	ClinicalTrials.gov identifier	Status
Suvorexant, zolpidem	Treatment of insomnia	PSP	3	NCT04014387	Active
Transcranial DC stim.	Electrical current stimulation	FTLD-*GRN*	N/A	NCT02999282	Active
Transcranial magnetic stim.	Magnetic field stimulation	PPA, bvFTD	N/A	NCT03406429	Active

ALS-C9orf72 amyotrophic lateral sclerosis due to chromosome 9 open reading frame 72 expansion, *AD* Alzheimer's disease, *bvFTD* behavioral variant frontotemporal dementia, *CBD* corticobasal degeneration, *FTLD* frontotemporal lobar degeneration, *FTLD-GRN* FTLD due to progranulin haploinsufficiency, *MAPT* microtubule-associated protein tau mutation, *nfvPPA* non-fluent variant primary progressive aphasia, *PPA* primary progressive aphasia, *PSP* progressive supranuclear palsy, *TES* traumatic encephalopathy syndrome

for upcoming trials in FTLD. ASOs are short, single-stranded, synthetic oligonucleotides that hybridize with high specificity to complementary pre-messenger RNA (mRNA) or mature mRNA and alter translations in a variety of ways [78]. These drugs require intrathecal delivery, but they offer an attractive diversity of mechanisms to suppress gene expression (mostly by triggering RNAaseH-mediated degradation of target mRNA), increase gene expression (by binding target promoters, suppressing microRNA, or suppressing natural antisense transcripts), or modulate alternative splicing (by forcing the inclusion or exclusion of specific exons). Additionally, previous trials in ASO-based therapies (NCT02193074, NCT00844597, NCT01396239/NCT01540409, and NCT02255552) have recently resulted in FDA approval of nusinersen [79] for treatment of spinomuscular atrophy (SMA) and eteplirsen [80] for treatment of Duchenne muscular dystrophy (DMD). Currently, BIIB080, an ASO that knocks down tau mRNA expression, is being investigated in patients with mild Alzheimer's disease (NCT03186989) and may have a role in future FTLD-tau trials. While human trial data has yet to be released, intrathecal infusion of BIIB080 resulted in 75% reduction of cortical *MAPT* mRNA and had no dose-limiting side effects in nonhuman primates [81]. An additional ASO-based strategy in FTLD-tau may include manipulation of alternative splicing of exon 10, which is included in the 4R forms of tau that predominate in PSP, CBD, and many pathogenic *MAPT* mutations adjacent to intron 10 or exon 10. So far, ASO-mediated splice alteration has been found to normalize the balance of 3R and 4R tau isoforms in a preclinical model [82] of pathogenic MAPT mutations, but this strategy has yet to be implemented in an active clinical trial program.

Multiple therapeutic trials have sought to limit pathogenic posttranslational modification of tau proteins using small molecule therapies. Salsalate is a repurposed small molecule (a nonsteroidal anti-inflammatory typically used to treat pain) that recently gained interest due its inhibition of potentially pathogenic tau acetylation. In preclinical studies, salsalate was found to inhibit tau acetylation via the p300 acetyltransferase and suppress tau accumulation in transgenic mice [83]. Salsalate was recently investigated in a phase 1 trial in PSP (NCT02422485), and while the drug was well tolerated, it failed to show a benefit compared to historic controls. Salsalate is now unlikely to be investigated in follow-up FTLD-tau trials, but a trial in Alzheimer's disease is still ongoing (NCT03277573). Other trial programs have investigated tideglusib and lithium carbonate, which potentially block tau phosphorylation via inhibition of glycogen synthase kinases (GSKs). Tideglusib failed to meet its primary endpoint of efficacy in a phase 2 trial [84]. Additionally, another small molecule therapy, ASN001, has been developed to inhibit O-GlcNAcylation of tau [85] (another potentially pathogenic posttranslational modification) but has yet to transition to an active trial. Several other small molecules have been developed to

inhibit tau accumulations directly. LMTM (TRx0237), a proprietary formulation of methylthioninium chloride (MTC), is a phenothiazine and perhaps the best clinically studied potential inhibitor of tau aggregation [86]. LMTM has so far failed to show benefits in primary endpoints of efficacy in large, multisite, phase 3 trials in both Alzheimer's disease [87] (NCT01689246) and bvFTD (NCT03446001).

An additional novel strategy for FTLD-tau treatment involves alteration of the extracellular milieu of injured neurons. Studies in aging mice suggest that plasma-derived factors from young mice may improve synaptic health, neurogenesis, and cognitive performance [88, 89]. In light of these findings, a small open-label phase 1 trial in PSP investigated the possible therapeutic benefit of plasma pooled from younger individuals (NCT02460731). This trial failed to show a therapeutic signal relative to historic controls, and whole plasma infusions are unlikely to be investigated in follow-up trials in FTLD-tau.

Future *C9orf72* Expansion Therapies

Pathogenic expansion of the *C9orf72* gene is the single most common genetic mutation causing familial frontotemporal dementia and ALS in North America and Europe [90]. Hexanucleotide expansions of *C9orf72* lead to FTLD pathology via a variety of possible mechanisms, including toxic gain of function from RNA-mediated toxicity and toxic dipeptides (from repeat-associated non-ATG translation) [91]. As discussed in a preceding section on future therapies for primary tauopathies, antisense oligonucleotide (ASO) therapies present a viable mechanism to degrade mRNA targets with high specificity. Intriguingly, in a preclinical rodent model of *C9orf72* expansion, ASOs targeting repeat-containing RNAs were sufficient to decrease toxic mRNA foci, suppress toxic dipeptide production, and improve cognitive performance [92]. Based on the preclinical success of this approach, BIIB078, an intrathecal ASO therapy targeting expanded *C9orf72* RNA, is now being studied in patients with ALS due to *C9orf72* expansion (NCT03626012). While this trial is not enrolling patients with FTD, any future success of this ALS therapeutic program is likely to translate patients with FTLD due to *C9orf72* expansion.

Progranulin Deficiency Therapies

Haploinsufficiency of the progranulin gene (*GRN*) is associated with an over 50% reduction in plasma and CSF progranulin levels and a high penetrance of FTD [93, 94]. Given the link between low progranulin levels and FTD, several therapeutic trials have sought methods to therapeutically raise progranulin in the blood and CSF. Based on preclinical mouse [95] and cell [96] models of progranulin deficiency, nimodipine (a calcium channel blocker) and histone deacetylase (HDAC) inhibitors were identified as possible oral therapies to increase progranulin levels. In an 8-week, open-label trial, nimodipine failed to raise progranulin levels in participants with *GRN* haploinsufficiency [95] (NCT01835665). Additionally, in a randomized double-blind placebo-controlled phase 2 trial, FRM-0334 (an HDAC inhibitor) also failed to raise plasma progranulin levels in participants with *GRN* haploinsufficiency (NCT02149160). So far more encouraging results have been reported in clinical human trials using AL001, a monoclonal antibody which blocks the sortilin receptor, an important component in the degradation of progranulin [97]. In a phase 1 open-label trial, AL001 successfully raised progranulin levels in healthy volunteers and individuals with *GRN* haploinsufficiency (NCT03636204). Additionally, AL001 appeared to decrease plasma neurofilament light chain levels in mutation carriers, thus providing an early signal of a possible neuroprotective effect [98]. AL001 has subsequently moved on to a phase 2 trial (NCT03987295), with plans for a phase 3 trial currently underway. Another potentially exciting mechanism of progranulin treatment is gene replacement therapy. While the details of these proposed therapeutic mechanisms remain proprietary, at least one potential approach has recently been publically discussed (PR006) which utilizes an AAV9-based vector to deliver a GRN replacement therapy [99].

Symptomatic Treatment Trials

While the majority of recent FTD clinical trial development has focused on disease-modifying interventions, a fair amount of recent trials have alternatively focused on novel strategies of symptom management. Due to encouraging results in a phase 1 study [100], the hormone oxytocin is currently being investigated in a phase 2 trial aimed at improving social apathy in patients with FTD (NCT01386333). Another current symptom management study is comparing the utility of suvorexant (a dual orexin receptor antagonist) to zolpidem (a GABA receptor agonist) in the treatment of insomnia secondary to PSP (NCT04014387). Additionally, a few novel non-pharmacological trials are underway, investigating transcranial electrical and magnetic stimulation techniques as methods of augmenting symptoms in FTD variants (NCT02999282, NCT03406429).

Conclusion

Patients with bvFTD and PPA may be treated with a wide array of current therapies. The current focus of bvFTD and PPA care involves dedicated non-pharmacological therapy, including patient/caregiver education, assessment of safety risks, and behavioral intervention strategies. Among pharmacological interventions, there is the strongest rationale for SSRIs as a means of improving undesired behaviors in bvFTD and PPA. Despite the lack of disease-modifying interventions for the underlying neuropathology of FTLD, there is currently a rich field of therapeutic strategies moving into clinical trials. While early tau immunotherapy trials have failed in FTLD-tau, there is a wide diversity of other therapeutic options available, including ASO therapies, inhibitors of pathogenic posttranslational modification of tau, and additional alternative immunological approaches. Within familial variants of FTD, there is also a growing portfolio of exciting possible therapies tailored to precise mechanisms of pathogenesis. These include possible ASO therapies in *C9orf72* expansion, anti-sortilin immunotherapy in *GRN* deficiency, and possible gene replacement therapy in *GRN* deficiency. Taken together, it is a truly exciting time for the field of FTLD treatment.

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