

REVIEW

The clinical spectrum of sporadic and familial forms of frontotemporal dementia

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The term frontotemporal dementia (FTD) describes a clinically, genetically and pathologically diverse group of neurodegenerative disorders. Symptoms of FTD can present in individuals in their 20s through to their 90s, but the mean age at onset is in the sixth decade. The most common presentation is with a change in personality and impaired social conduct (behavioural variant FTD). Less frequently patients present with language problems (primary progressive aphasia). Both of these groups of patients can develop motor features consistent with either motor neuron disease (usually the amyotrophic lateral sclerosis variant) or parkinsonism (most commonly a progressive supranuclear palsy or corticobasal syndrome). In

about a third of cases FTD is familial, with mutations in the progranulin, microtubule-associated protein tau and chromosome 9 open reading frame 72 genes being the major causes. Mutations in a number of other genes including TANK-binding kinase 1 are rare causes of familial FTD. This review aims to clarify the often confusing terminology of FTD, and outline the various clinical features and diagnostic criteria of sporadic and familial FTD syndromes. It will also discuss the current major challenges in FTD research and clinical practice, and potential areas for future research.

Keywords: amyotrophic lateral sclerosis, *C9ORF72*, frontotemporal dementia, progranulin, tau.

J. Neurochem. (2016) **138** (Suppl. 1), 6–31.

This article is part of the [Frontotemporal Dementia special issue](#).

Frontotemporal dementia (FTD) is a clinically and pathologically diverse group of progressive neurodegenerative disorders leading to changes in behaviour, social conduct, language or speech because of atrophy of the frontal or anterior temporal lobes of the brain (or both). Although it occurs less frequently than Alzheimer's disease (AD), FTD is a common cause of young onset dementia, often affecting individuals below the age of 65 years. However, it also affects older individuals, and may be under-diagnosed because of individuals being misdiagnosed with AD or other types of dementia (Onyike and Diehl-Schmid 2013). The majority of cases have no known cause ('sporadic' FTD), but approximately a third is familial, secondary to autosomal dominant mutations in one of several FTD-associated genes. There are two main clinical subtypes found in patients presenting with FTD: behavioural variant FTD (bvFTD), which primarily affects behaviour and social interaction, and primary progressive aphasia (PPA), which causes progressive impairment of speech and language. Both sporadic and familial FTD patients can also develop concurrent motor neuron disease (MND) (Devenney *et al.* 2015) or an atypical parkinsonian disorder such as corticobasal syndrome (CBS) or a progressive supranuclear palsy

syndrome (PSPS) (Espay and Litvan 2011; Kertesz *et al.* 2011; Park and Chung 2013).

Despite a wealth of studies on FTD, much remains unknown about the disease, including the cause of the sporadic form. This is partly because of the heterogeneity of clinical presentation, age at disease onset and speed of progression. In addition, there is a wide diversity of underlying neuropathology in patients with similar clinical presentations, and lack of clinicopathological correlation in the majority of patients. The overlap with other neurological syndromes makes the disease even more complex. In this review we aim to clarify the terminology of FTD, outline the

Received February 18, 2016; revised manuscript received April 10, 2016; accepted April 27, 2016.

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Abbreviations used: ALS, amyotrophic lateral sclerosis; bvFTD, behavioural variant FTD; CBS, corticobasal syndrome; FTD, frontotemporal dementia; LPA, logopenic aphasia; MND, motor neuron disease; PPA, primary progressive aphasia; PSPS, progressive supranuclear palsy syndrome; svPPA, semantic variant PPA; VCP, valosin containing protein.

various clinical features and diagnostic criteria of sporadic and familial FTD syndromes and discuss the current major challenges in FTD research and clinical practice. We also outline potential areas for future research.

Terminology

Frontotemporal dementia and frontotemporal lobar degeneration

The terminology of FTD can be confusing, and has evolved significantly since the first description of a patient with progressive language disturbance and left superior temporal gyrus atrophy by Pick (1892). Histopathological presence of argyrophilic globular neuronal cytoplasmic inclusions (later termed Pick bodies) was actually described not by Pick but by Alzheimer (1911) and the concept of FTD as ‘Pick’s disease’ by a Dutch group (Gans 1925) and by a German group (Onari and Spatz 1926). By 1956, it had become evident that true Pick’s pathology was underlying only around 20% of clinical FTD cases (Escourolle 1958) and subsequent studies confirmed that there were multiple other pathologies associated with atrophy of the frontal and/or temporal lobes in patients with the clinical syndrome of FTD (Brun 1987; Mann *et al.* 1993). The historical term for bvFTD, Pick’s disease, is now reserved for cases of FTD with Pick type pathology. The term ‘frontotemporal lobar degeneration’ (FTLD) was therefore designated to describe a heterogeneous group of neurodegenerative diseases characterized by selective frontal and/or temporal lobe atrophy (Neary *et al.* 1998), and who have non-Alzheimer’s disease neuropathology (Lashley *et al.* 2015).

Behavioural and language variants

It is now well recognized that there are two main initial clinical presentations seen in patients with FTD: bvFTD describes those who develop progressive behavioural change, inappropriate social conduct and executive dysfunction, and PPA describes those who have progressive language decline and speech difficulties. There are three variants of PPA: semantic variant PPA (svPPA) leading to fluent speech with anomia, impaired single word comprehension and surface dyslexia due to loss of semantic memory; non-fluent (or agrammatic) variant PPA (nfvPPA), leading to effortful speech production with agrammatism, apraxia of speech and impaired sentence comprehension; and logopenic variant PPA (lvPPA) leading to word-finding pauses and impaired sentence repetition (Gorno-Tempini *et al.* 2011). LvPPA is mostly associated with AD pathology and is therefore not always included within the FTD spectrum, while in a minority of cases it can be associated with FTLD pathology (Lashley *et al.* 2015).

FTD is now used as an umbrella term to describe the overall group of clinical syndromes, while it has previously been used to just mean the progressive behavioural syndrome

now called bvFTD (Neary *et al.* 2005). Other terms used previously for this include frontal lobe dementia (Lund and Manchester Groups 1994) and frontal variant FTD. Evolution of PPA terminology has been more tortuous. Despite Pick’s original FTD case being a patient with language difficulties (Pick 1892) and reports of a variant of FTD with predominant language or speech decline published in the early 20th century, explicit description and widespread acceptance of a language-led variant of FTD remained elusive until the 1970s. In 1975, Warrington characterized the presentation of patients with selective deficits in semantic memory, leading to the later description of semantic dementia (Snowden *et al.* 1989; Hodges *et al.* 1992). Mesulam (1982) also described a slowly progressive selective aphasia, later labelling this syndrome as PPA (Mesulam 1987). In an early consensus document of diagnostic criteria for behavioural and language variants of FTD, PPA was initially split into a fluent subtype (semantic dementia) and a non-fluent subtype (progressive non-fluent aphasia) (Neary *et al.* 1998). However, another subtype of PPA was subsequently recognized, called logopenic aphasia (LPA) or the logopenic/phonological variant of PPA (Gorno-Tempini *et al.* 2004, 2008), and this was subsumed into the most recent consensus diagnostic criteria for PPA (Gorno-Tempini *et al.* 2011) which recognizes three variants: nfvPPA, svPPA and lvPPA. The nosology of the FTD spectrum is not entirely resolved and several studies of PPA have identified a group of patients that do not fit criteria for any of the three described variants (Sajjadi *et al.* 2012, 2014; Wicklund *et al.* 2014).

Overlap syndromes

In patients with overlap syndromes of FTD with MND, PSPS or CBS, behavioural and cognitive symptoms can develop before, after or simultaneously with motor symptoms (Kertesz *et al.* 2011; Park and Chung 2013; Siuda *et al.* 2014; Devenney *et al.* 2015). In clinical practice, there is often controversy or indecision about what diagnosis to give, or whether to revise the diagnosis when new symptoms appear, to capture this development of a new mixed phenotype. For example, a patient presenting with behavioural changes consistent with bvFTD who later develops falls, supranuclear gaze palsy and axial rigidity, may have their diagnosis changed to PSPS. Similarly, a patient with initial language dysfunction characterized by effortful and agrammatic speech, who is first diagnosed with nfvPPA, but later develops asymmetric limb apraxia, rigidity and myoclonus, may be later re-diagnosed with CBS. In our experience, this changing of the diagnosis can be confusing for patients and their families (‘was the initial diagnosis wrong?’), and from a research point of view can lead to loss of important phenotypic information (e.g. in pathological or genetic studies it may be important to distinguish between PSPS cases who develop PPA and those who develop bvFTD). We would advocate the use of overlap terms such as

PPA-CBS or FTD-PPSPS to help clarify such confusion, as has been done with MND: patients with FTD who later develop MND are usually diagnosed with FTD-MND (or FTD-ALS), and those with initial MND and symptoms that later fit criteria for bvFTD or PPA are labelled as MND-FTD (or ALS-FTD). However, overlap of these disorders can be variable and one unresolved dilemma is how to classify patients that do not quite fulfil criteria for a particular disorder but have mild features. Although around 10–15% of patients with FTD develop MND (Lomen-Hoerth *et al.* 2002; Burrell *et al.* 2011), there is an even higher prevalence of ‘subclinical’ evidence of MND, with electromyogram evidence of MND or subtle MND-like clinical signs, such as fasciculations, in 60% of FTD patients (Lomen-Hoerth *et al.* 2002). Conversely, while 10–20% of MND patients meet diagnostic criteria for FTD, at least 50% of patients presenting with MND develop cognitive or behavioural impairment, termed MNDci (or ALSci) and MNDbi (or ALSbi) (Strong *et al.*, 2009). Of the various MND phenotypes seen in FTD patients, the majority usually develop the ALS variant, but lower motor neuron (primary muscular atrophy) or upper motor neuron (primary lateral sclerosis) phenotypes are also seen rarely (Devenney *et al.* 2015). As with MND, patients with FTD may develop parkinsonian features (bradykinesia, rigidity, tremor and/or postural instability) not fully consistent with a particular clinical syndrome such as PSPS or CBS, and are often diagnosed with FTD with parkinsonism. Parkinsonism is seen in around 20% of patients, while a larger proportion may eventually develop this in end-stage disease (Park and Chung 2013). One large study of 364 FTD cases (35 with pathological confirmation), demonstrated the presence of parkinsonism as an early feature in 16% (18% of bvFTD, 14% of nvPPA and 11% of svPPA) (Seelaar *et al.* 2008). Very rarely, patients develop FTD, MND and parkinsonism, including some patients with an underlying *C9ORF72* expansion mutation (Coon *et al.* 2011; Boeve *et al.* 2012; Mahoney *et al.* 2012; O’Dowd *et al.* 2012; Snowden *et al.* 2012).

Sporadic versus familial FTD

Currently, the only confirmed risk factors for FTD are mutations in certain genes. Between 30% and 50% of patients report a positive family history of FTD in at least one family member and a clearly autosomal dominant inheritance pattern is seen in 10–15% of patients (Goldman *et al.* 2005; Rohrer *et al.* 2009a). BvFTD is significantly more heritable than PPA, with nvPPA being much more likely to be familial than svPPA (Rohrer *et al.* 2009a). CBS can be familial in some cases, and PSP is only very rarely familial. Estimates of heritability of FTD-MND vary widely between studies and it remains unclear how many cases are genetic.

Mutations in three genes account for the majority of familial FTD, predominantly through autosomal dominant inheritance: progranulin (*GRN*) (Baker *et al.* 2006; Cruts

et al. 2006), microtubule-associated protein tau (*MAPT*) (Wilhelmsen *et al.* 1994; Hutton *et al.* 1998) and the chromosome 9 open reading frame 72 (*C9ORF72*) (DeJesus-Hernandez *et al.* 2011; Renton *et al.* 2011). More recently, mutations in TRAF tumour necrosis factor receptor-associated factor family member-associated NF-kappa-B activator (TANK)-binding kinase 1 (*TBKI*) have been identified in association with familial FTD (Freischmidt *et al.* 2015; Gijssels *et al.* 2015; Le Ber *et al.* 2015; Pottier *et al.* 2015). Small numbers of patients possess mutations in other rare, FTD-associated genes. Mutations in valosin containing protein (*VCP*)-1 are usually associated with a multisystem proteinopathy manifesting as inclusion body myopathy and Paget’s disease of the bone (Watts *et al.* 2004), and mutations in charged multi-vesicular body protein 2B (*CHMP2B*) (Skibinski *et al.* 2005) are found mainly in a Danish cohort. Rare genetic causes of FTD include transactive response DNA-binding protein-43 (*TARDBP*) (Synofzik *et al.* 2014), ubiquilin 2 (*UBQLN2*) (Gellera *et al.* 2013), p62/sequestome1 (*SQSTM1*) (Rubino *et al.* 2012; Le Ber *et al.* 2013; Miller *et al.* 2015), fused in sarcoma (*FUS*) (Kwiatkowski *et al.* 2009; Vance *et al.* 2009), dynactin-1, associated with Perry syndrome (Munch *et al.* 2005) and coiled-coil-helix-coiled-coil-helix domain containing 10 (*CHCHD10*) (Bannwarth *et al.* 2014). Mutations in presenilin-1 or amyloid precursor protein, both associated with familial AD, and prion protein, associated with familial prion disease, have also been associated with a clinical FTD syndrome (Rohrer and Warren 2011). A small proportion of patients (1.2% in one study of 334 patients) (van Blitterswijk *et al.* 2013) have dual mutations, for example, the *C9ORF72* expansion as well as another mutation in one of the other FTD genes, for example, *GRN* (Lashley *et al.* 2014).

Clinical syndromes of FTD

In this section we summarize the clinical features of bvFTD and PPA variants, with reference to most recent diagnostic consensus criteria (Gorno-Tempini *et al.* 2011; Rascovsky *et al.* 2011). Specific features of the various familial FTD phenotypes will be discussed in the later section entitled ‘Clinical syndromes of familial FTD’.

Behavioural variant FTD

BvFTD presents with progressive decline in social skills, difficulties with planning and higher level thinking due to executive dysfunction and distinct changes in behaviour with relative preservation of other cognitive areas such as episodic memory and visuospatial function in the early stages. Patients with a PPA subtype or PSPS/CBS overlap disorder can also display similar behavioural features, as discussed below, but by definition they are not predominant at initial presentation. Patients with bvFTD often lack insight into their problems, and may seem indifferent or annoyed when

brought to medical attention as they feel that there is nothing the matter with them. It is usually the patients' relatives or close friends who notice that something is wrong, usually because of a breakdown in their relationship with the patient or complaints from friends or work colleagues about odd behaviour or increasingly poor performance at work. Relatives' reports of the patient having a 'poor memory' usually refer more to their perception of a change in the patient's level of personal and social functioning rather than true memory problems, and unfortunately can lead to a misdiagnosis of AD or repeated misdiagnoses such as 'stress', anxiety or depression by the non-specialist. Careful questioning in clinic, and particularly of the accompanying relative when they are alone, will reveal the true nature of cognitive changes and a history of progression of symptoms over time, both essential for aiding correct diagnosis.

The most recent diagnostic criteria for bvFTD (Rascovsky *et al.* 2011) were developed by the Frontotemporal Dementia Consortium to summarize more succinctly the key features of behavioural change seen in this subtype, while recognizing that other cognitive features such as episodic memory can be affected, albeit less commonly. Criteria for a diagnosis of possible bvFTD are displayed in Table 1; patients must attain any three out of the six key clinical features: five behavioural (disinhibition, apathy or inertia, loss of sympathy or empathy, stereotyped or compulsive behaviours or hyper-orality) and one cognitive (predominant executive dysfunction on neuropsychological assessment). The sensitivity and specificity of these diagnostic criteria for correct diagnosis of bvFTD have been reviewed in a number of studies with confirmation of FTLD or non-FTLD pathology, which have established that the criteria have 85–95% sensitivity and 82% specificity for a diagnosis of possible bvFTD and 75–85% sensitivity and 95% specificity for probable bvFTD (Rascovsky *et al.* 2011; Harris *et al.* 2013b).

There are a number of clinical features, however, which are not part of the Rascovsky criteria and yet are relatively common in bvFTD. In particular, virtually all patients with bvFTD have impaired social cognition, with reduced ability to use a 'theory of mind' to see another person's point of view or imagine their feelings (Kumfor and Piguet 2012). Several studies have shown that patients with bvFTD also display significant impairments in emotion recognition, even when tested across multiple modalities, and have more difficulty recognizing negative emotions (Lavenex *et al.* 1999; Rosen *et al.* 2004; Fernandez-Duque and Black 2005; Lough *et al.* 2006). They also have difficulty in expressing meaningful emotions, resulting in 'emotional blunting' (Neary *et al.* 1998; Sturm *et al.* 2011).

Several groups have observed altered perception of surrounding environmental and internal somatosensory stimuli, including changes in tolerance of pain or temperature. Patients with bvFTD tend to have blunted perception of pain (Bathgate *et al.* 2001; Snowden *et al.* 2001; Carlino *et al.*

2010; Fletcher *et al.* 2015) and temperature (Ahmed *et al.* 2015; Fletcher *et al.* 2015). In bvFTD patients this can anecdotally manifest as wearing inappropriately heavy clothing or blankets in a warm clinic. Others have developed altered perception of sound or music (Seeley *et al.* 2008; Warren and Rohrer 2009; Barquero *et al.* 2010; Mahoney *et al.* 2011; Fletcher *et al.* 2013), with some patients merely developing heightened sensitivity to noise (Fletcher *et al.* 2013) and others frank musicophilia (Fletcher *et al.* 2013) or amusia (Barquero *et al.* 2010). These phenomena suggest that a variety of networks involved in sensory input processing and integration may be affected in FTD.

Neuropsychiatric manifestations such as delusions or hallucinations are found in sporadic bvFTD and may be the sole presentation in patients with familial bvFTD (particularly those with *C9ORF72* or *GRN* mutations, as discussed later). In a review of 751 cases of FTD published in 199 publications from 1950 to 2007, 46 (6%) of patients presented with schizophrenia, schizoaffective disorder, bipolar affective disorder, psychotic depression or another psychotic disorder; with 98% of these patients presenting aged < 60 (Velakoulis *et al.* 2009). In another large study of patients with a variety of neurodegenerative disorders, including bvFTD, nfvPPA, svPPA, AD, PSPS, CBS and ALS, 28.5% of patients had received a previous psychiatric diagnosis (usually depression), and this was much more common in patients who turned out to have bvFTD (50.7%) than nfvPPA (11.8%), svPPA (24.4%) or AD (23.1%) (Woolley *et al.* 2011). The typical previous psychiatric diagnosis in bvFTD patients in this study was schizophrenia or bipolar disorder. Young onset apparently sporadic bvFTD cases with FUS pathology have a particularly high (up to 50%) rate of psychiatric symptoms. The lack of other cognitive or neurological features early on commonly leads to young and older patients with sporadic and familial bvFTD being referred to and assessed within a psychiatric or psychogeriatric setting rather than in a specialist cognitive neurology or memory clinic (Lanata and Miller 2015). The obvious overlap between early bvFTD symptoms (lack of insight, prominent apathy, obsessive or compulsive behaviours, inappropriate sexual behaviour, binge eating, gambling and substance misuse, emotional lability or blunting, delusions and hallucinations) and psychiatric presentations (depression, obsessive-compulsive disorder, bipolar affective disorder and schizophrenia and other psychotic disorders) can initially lead to misdiagnosis of a neurodegenerative disease as a psychiatric disorder. Younger patients with 'later than usual' onset of neuropsychiatric disease, atypical or prominent behavioural features and any suggestion of multiple family members with significant psychiatric disease (e.g. needing long-term or permanent admission to a mental health facility), 'early onset dementia', AD, FTD or MND, should be carefully assessed with a neurological examination, detailed family history and,

Table 1 Summary of behavioural and cognitive symptoms within the current diagnostic criteria for behavioural variant frontotemporal dementia (bvFTD) and other commonly seen features

Behavioural/cognitive symptoms – diagnosis of possible bvFTD requires at least three of the following symptoms to be fulfilled:		Examples of specific symptoms
Early behavioural disinhibition ≥ 1 of		
Socially inappropriate behaviour		Staring, inappropriate physical contact with strangers, inappropriate sexual behaviour, verbal or physical aggression
Loss of manners or decorum		Lack of social etiquette, insensitive or rude comments, preference for crass jokes and slapstick humour, inappropriate choices of clothing or gifts
Impulsive, rash or careless actions		New gambling behaviour, driving or investing recklessly, overspending, gullibility to phishing/Internet scams
Early apathy or inertia ≥ 1 of		
Apathy		Reduced drive, stops previous hobbies, stops going out, reduced bathing or personal care
Inertia		Lack of persistence or completion of an activity, does not initiate activities or conversations
Early loss of sympathy or empathy ≥ 1 of		
Diminished response to other people's needs and feelings		Selfish or hurtful comments or actions, inability to perceive when someone is upset, embarrassed, or in pain, reduced appreciation of sarcasm or sophisticated humour
Diminished social interest, interrelatedness, or personal warmth		Emotionally cold or detached, lack of rapport in conversation, loss of interest or affection in relationships with friends or family members, reduced interest in sex
Early perseverative, stereotyped or compulsive or ritualistic behaviour ≥ 1 of		
Simple repetitive movements		Repetitive rocking, tapping, clapping, or rubbing
Complex compulsive or ritualistic behaviours		Hoarding, strict grooming or walking routines, timekeeping and counting, checking or sorting items, cleaning or tidying, new obsessions or interests (usually spiritual, religious, artistic, or musical)
Stereotypy of speech		Habitual repetition of particular words, sentences or topics
Hyperorality and dietary changes ≥ 1 of		
Altered food preferences		Sweet tooth (sweets, biscuits, ice cream), carbohydrates, or obsessive food fads
Binge eating, increased consumption of alcohol or cigarettes		Cramming food into mouth, overeating or messy eating, new addictions to alcohol or smoking
Oral exploration or consumption of inedible objects		Pica
Neuropsychological profile – all three of		
Deficits in executive tasks		Vary as per neuropsychological assessment used
Relative sparing of episodic memory		
Relative sparing of visuospatial skills		
Other features of bvFTD (not in diagnostic criteria)		
		Examples of specific symptoms
Loss of insight		Lack of awareness of own condition or symptoms
Impaired social cognition		Poor response to social or emotional cues; impaired performance on tests of theory of mind or emotion recognition
Altered sensitivity to pain		Heightened perception of a non-painful stimulus or reduced response to painful stimulus; hypochondriasis or overly focusing on mild physical complaints
Altered tolerance of temperature		Inappropriate clothing for the ambient temperature, such as wearing multiple coats or blankets
Psychotic features		Delusions (usually somatic or paranoid) and hallucinations (usually visual or tactile)

Table content is adapted from Rascovsky *et al.* (2011) and Warren *et al.* (2013). To qualify for a diagnosis of possible bvFTD, patients need to have a progressive deterioration of behaviour and/or cognition as per observation or history from an informant, and must possess persistent evidence of least three of the six main groups of behavioural/cognitive symptoms as listed above. The term 'early' refers to within 3 years of initial symptom onset as per Rascovsky *et al.* (2011).

wherever possible, formal neuropsychology and detailed magnetic resonance imaging (MRI).

Patients with bvFTD classically have preserved episodic memory, at least early on in disease, helping differentiation from AD, but this is not always the case. Patients often have deficits in verbal and visual memory on neuropsychological assessment, even if they do not report memory problems; their performance is often worsened by poor strategy during assessments because of concurrent executive dysfunction and distractibility. However, a significant proportion of pathologically confirmed bvFTD cases have presented with a predominant amnesic syndrome (Hodges *et al.* 2004; Graham *et al.* 2005; Piguet *et al.* 2009; Irish *et al.* 2013), perhaps because of a higher occurrence of hippocampal sclerosis in the older age group (Baborie *et al.* 2011; Balasa *et al.* 2015) or mixed pathology (Balasa *et al.* 2015). This emphasizes the difficulties clinicians face in making a correct diagnosis, particularly in later onset cases, despite using currently available consensus criteria.

The requirements for functional decline and neuroimaging abnormalities for diagnosing probable bvFTD, compared with previous diagnostic criteria (Neary *et al.* 1998), are particularly useful for excluding patients with a so-called phenocopy syndrome, who may have bvFTD-like symptoms but do not have bvFTD. Relatives of patients with phenocopies often seem certain that there is progression over time, but most neuropsychological assessments tend to dispute this, often showing normal values or mild but stable impairment (Hornberger *et al.* 2009). These patients have no or minimal atrophy on MRI and normal nuclear medicine imaging with PET (positron emission tomography) or SPECT (Single-photon emission computed tomography) scans, and either remain stable or improve over time, without significant disruption of function (Davies *et al.* 2006). Previous diagnostic criteria for bvFTD (Neary *et al.* 1998) potentially allowed phenocopy cases to be falsely diagnosed as having bvFTD, as they presented almost identically on core diagnostic criteria (Hornberger *et al.* 2009), and these cases are notoriously difficult to tell apart, particularly at initial assessment. Repeated assessments of functional abilities over a 12-month period (Mioshi and Hodges 2009), neuropsychological assessments of executive function (Hornberger *et al.* 2008) and social cognition (Kipps *et al.* 2009b), and neuroimaging using combined MRI and FDG-PET (Kipps *et al.* 2009a) appeared most helpful in differentiating phenocopy syndromes from true bvFTD, hence their incorporation into the revised criteria (Rascovsky *et al.* 2011). One proviso to this is that some patients can occasionally actually have an atypical, very slowly progressive form of FTD, with very slow deterioration on repeated neuropsychological assessments over at least 15 years, and neuropathological confirmation of typical FTLD pathology (Brodtmann *et al.* 2013), which further confuses the clinical picture.

Primary progressive aphasia

The key clinical characteristic of PPA is progressive and insidious language decline affecting at least one of speech production, object naming, syntax, or word comprehension (Gorno-Tempini *et al.* 2011). Other cognitive or behavioural deficits can develop either early on or in late disease, but must not be the initial and predominant complaint and language must also remain the most impaired domain throughout the disease course (Mesulam 1982, 2003). The most recent diagnostic criteria for PPA have specified that three inclusion criteria, based on criteria developed by Mesulam (1982, 2001, 2003), must first be fulfilled for its diagnosis (Gorno-Tempini *et al.* 2011): (i) the most prominent clinical feature is difficulty with language, (ii) these deficits are the principal cause of impaired daily living activities and (iii) aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease. In addition, none of the following criteria should be met: (i) the pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders (e.g. tumour or stroke); (ii) the cognitive disturbance is better accounted for by a psychiatric diagnosis; (iii) there are prominent initial episodic memory, visual memory and visuo-perceptual impairments and (iv) there is prominent, initial behavioural disturbance. Once these inclusion and exclusion criteria have been satisfied, one can go on to subdiagnose the syndrome as one of three PPA variants (svPPA, nfvPPA or lvPPA), as per diagnostic criteria for each variant (see Gorno-Tempini *et al.* 2011, for a summary). Clinical diagnosis can be supplemented by information from neuroimaging analyses (leading to the more firm category, 'imaging-supported diagnosis'). If there is a clinical diagnosis of PPA (with or without neuroimaging support) and presence of either a known pathogenic gene mutation on DNA analysis or specific neurodegenerative pathology on histopathological analysis, this leads to a diagnosis of PPA 'with definite pathology'.

Different language features can be used to differentiate between the three variants and these are summarized in Table 2. However, not all patients clearly fit into a particular variant as they present with a number of features from across the spectrum of language dysfunction, and previously have been termed as having mixed disease (PPA-M) (Mesulam *et al.* 2009). More recently patients have been diagnosed with 'PPA-not otherwise specified' and over time the evolving syndrome may or may not become clearer (Harris *et al.* 2013b), while some are associated with a *GRN* mutation (Rohrer *et al.* 2010a). There is also a syndrome within the non-fluent aphasia spectrum called progressive primary apraxia of speech, which progressively affects speech articulation and production because of impaired motor programming, but typically patients lack aphasia initially (Josephs *et al.* 2012). It can be associated with development of features of PSPS (Rohrer *et al.* 2010b;

Table 2 Summary of clinical features across the syndromes of primary progressive aphasia

Clinical features	svPPA	nvPPA	lvPPA
Spontaneous speech (fluency, errors, grammar, prosody)	Fluent, garrulous and circumlocutory, semantic errors, intact grammar and prosody	Slow and hesitant, effortful \pm apraxic, phonetic errors, may be agrammatic, aprosodic	Hesitant, not effortful or apraxic, frequent word-finding pauses and loss of train of sentence, intact grammar, intact prosody
Naming	Severe anomia with semantic paraphasias	Moderate anomia with phonetic errors and phonemic paraphasias	Mild to moderate anomia with occasional phonemic paraphasias
Single word comprehension	Poor	Intact early on, but affected later on	Intact early on, but affected later on
Sentence comprehension	Initially preserved, later on becomes impaired as word comprehension is impaired	Impaired if grammatically complex	Impaired, especially if long
Single word repetition	Relatively intact	Mild to moderately impaired if polysyllabic, otherwise intact	Relatively intact (compared with sentence repetition)
Sentence repetition	Relatively intact	Can be effortful, impaired if grammatically complex	Impaired, with length effect
Reading	Surface dyslexia	Phonological dyslexia \pm phonetic errors on reading aloud	Phonological dyslexia
Writing	Surface dysgraphia	Phonological dysgraphia	Phonological dysgraphia

svPPA, semantic variant primary progressive aphasia; nvPPA, non-fluent variant primary progressive aphasia; lvPPA, logopenic variant primary progressive aphasia. Clinical features are adapted from tables in Rohrer *et al.* (2008, 2010a), Seelaar *et al.* (2011) and Gorno-Tempini *et al.* (2011).

Josephs *et al.* 2014) or, less frequently, CBS (Josephs and Duffy 2008; Assal *et al.* 2012). Here, we discuss the clinical features of each PPA variant in turn, the language and behavioural features that overlap between them and with bvFTD, the presence of other common clinical features and the overlap with other conditions such as PSPS, CBS and MND.

SvPPA

SvPPA accounts for around 20% of cases of FTD (Johnson *et al.* 2005). It is a predominantly sporadic disorder (Rohrer *et al.* 2009a) and presents with a mean age of onset of 60, with a range of 40–79 years (Hodges *et al.* 2010), although is likely under-diagnosed in older people, particularly as the semantic memory deficits can develop insidiously and are usually well-masked by the perception of fluent speech, and use of commonly used empty speech terms such as ‘thing’ (Fletcher and Warren 2011; Hsieh *et al.* 2012). It is associated with not only bilateral, but markedly asymmetrical anterior temporal lobe atrophy at presentation, particularly affecting the inferior and middle temporal gyri, but also the anterior hippocampus and amygdala (Hodges *et al.* 1992; Mummery *et al.* 1999, 2000; Whitwell *et al.* 2005; Rohrer *et al.* 2009b). The majority of patients present with predominant left temporal lobe atrophy, which leads to the classical language disorder of svPPA, characterized by early loss of semantic memory and resultant language dysfunction (Snowden *et al.* 1989; Hodges *et al.* 1992). Less frequently patients present with predominant right temporal lobe atrophy at onset, often called right temporal lobe atrophy

(RTLA) FTD or ‘right SD’ cases (Evans *et al.* 1995; Thompson *et al.* 2003; Chan *et al.* 2009). The language impairment in svPPA initially manifests as reduced semantic knowledge for words, objects and concepts, which affects spoken and written language through development of a reduced vocabulary and resultant anomia (Warrington 1975). As atrophy worsens and extends across to the right temporal lobe and to the inferior frontal lobe, insula, and more posterior left temporal lobe (Seeley *et al.* 2005; Brambati *et al.* 2009), it impairs semantic function across multiple modalities, leading to associative agnosia for visual, auditory (Bozeat *et al.* 2000; Goll *et al.* 2010), tactile (Coccia *et al.* 2004), olfactory (Rami *et al.* 2007) and gustatory (Piwnica-Worms *et al.* 2010) stimuli. Patients lose their grasp for increasingly imprecise or broad semantic terms and concepts, with responses to stimuli becoming more general (e.g. ‘poodle’-->‘dog’--> ‘animal’--> ‘don’t know’) over time.

Patients with svPPA generally report word-finding difficulties, which may start off as being only for specialist, low-frequency (rarely used) words (such as names of flowers for a gardener, or facial anatomical terms for a dentist). This worsens to affect commonly used words. Patients may ask relatives to explain the meaning of a word someone has said or that they have read (Fletcher and Warren 2011; Warren *et al.* 2013), which at first is usually an unusual word, such as ‘orangutan’. Relatives may report the patient does not seem to understand what is being said to them, or ‘appears deaf’, asking for instructions to be repeated several times (Rohrer *et al.* 2008). Clinically, the language dysfunction in

svPPA is characterized by fluent speech, which is often garrulous or difficult to interrupt but has frequent circumlocutions (e.g. 'thing' or 'whatsit'), circumlocutory phrases (imprecise phrases that contain vague descriptions or explanations of the word aimed for, e.g. 'the thing with the tail that you ride' for 'horse') and semantic paraphasias (similar but incorrect words often from within the same category, e.g. 'cat' for 'dog'), used by the patient to work around their lack of vocabulary (Hodges and Patterson 2007). There can be brief hesitations during word-finding moments, but overall the speech is much more fluent than the effortful speech in nvPPA or speech with significant pauses in lvPPA. On assessment, patients have anomia on confrontation naming tasks (which may appear subtle without detailed probing by a full neuropsychological assessment), and impaired comprehension of the meaning of single words, particularly on low-frequency items such as 'monocle'. Later on, there is anomia and impaired comprehension of pictures, sounds, smells and tastes. Patients often have difficulties with reading and writing, particularly with irregularly spelt words, leading to the phenomenon of a surface dyslexia or surface dysgraphia (Warrington 1975; Baxter and Warrington 1987). For example, patients will pronounce 'sew' as 'soo' or 'yacht' as 'yatched', as they have lost semantic knowledge of the word meaning (and hence the atypical rule for how it should be pronounced), relying on sounding out the word as written using superficial rules only (Rohrer *et al.* 2008). Other cognitive domains are usually unaffected, including episodic and topographical memory, visuo-perceptual function, praxis, calculation and non-verbal executive function (Warrington 1975; Cipolotti and Maguire 2003; Gordon *et al.* 2010). Other aspects of language such as speech articulation and prosody, and repetition of spoken words and phrases are also usually preserved. Grammar is intact, although as vocabulary declines, grammar can sound abnormal, because of the use of 'paragrammatic', circumlocutory phrases and broad classes of terms, which disrupt the normal flow of the sentence (Gorno-Tempini *et al.* 2011).

Patients with typical svPPA evolve over time (due to spread of disease) to develop behavioural changes, which can make it difficult to differentiate these patients from bvFTD patients clinically if presenting late in the disease. However, behavioural changes particularly found in typical svPPA include obsessionality, mental rigidity, narrowed interests (often affecting eating behaviour, daily routines and fixations on specific activities, e.g., jigsaw puzzles) (Snowden *et al.* 2001; Thompson *et al.* 2003), more compulsive and complex repetitive behaviours (Snowden *et al.* 2001), heightened perception of pain and sensory stimuli leading to hypochondriasis and increased sensitivity to temperature (Fletcher *et al.* 2015). Cases of svPPA with altered auditory perception such as hyperacusis and persistent tinnitus (of central rather than peripheral origin) have also been observed (Mahoney *et al.* 2011).

Patients with the right temporal variant can be difficult to identify purely from a clinical assessment as they often have early behavioural changes and less prominent semantic difficulties initially (Chan *et al.* 2009). The key distinguishing feature of RTLA cases is early prosopagnosia (impaired recognition of familiar faces) (Tyrrell *et al.* 1990; Evans *et al.* 1995; Gainotti *et al.* 2003; Thompson *et al.* 2003; Joubert *et al.* 2006), but when compared with cases with predominant left temporal lobe atrophy, RTLA cases also report more difficulties with topographical memory (potentially due to right hippocampal atrophy) (Chan *et al.* 2009), and may have a more bizarre affect (Thompson *et al.* 2003). They also tend to have less insight into their disease (Thompson *et al.* 2003) and can develop other unusual features such as hyper-religiosity (Edwards-Lee *et al.* 1997; Chan *et al.* 2009). Not all RTLA patients will develop semantic impairment and initial studies have suggested that there are at least two RTLA variants: one that is the mirror analogue of svPPA with disease spread occurring inter-hemispherically to the left temporal lobe, and another with behavioural symptoms where atrophy spreads intra-hemispherically, predominantly affecting the right frontal and parietal lobe (Kamminga *et al.* 2015). These tend to have differing underlying pathologies as well: the right SD cases have FTLT-DTP type C pathology, whereas patients with bvFTD rarely have this subtype (Rohrer *et al.* 2011a; Lashley *et al.* 2015), potentially affecting accurate targeting of future treatments towards the different disease groups.

NfvPPA

Approximately 25% of patients with FTD present with nvPPA (Johnson *et al.* 2005). The classical neuroimaging feature is atrophy of the left posterior (and inferior) frontal lobe and insular cortex (Rohrer *et al.* 2009b). In contrast to the fluent aphasia observed in svPPA, patients with nvPPA have non-fluent speech, with the two core features being agrammatism and slow laboured speech production ('effortful speech') (Gorno-Tempini *et al.* 2011). In some patients the former impediment is dominant, and in others, the latter, but in most cases the disease evolves to result in both features (Rohrer *et al.* 2010c). Patients with nvPPA tend to present earlier than patients with svPPA, as speech is obviously disrupted and sounds abnormal early on (Hsieh *et al.* 2012). Importantly, single word comprehension and object knowledge are preserved, as semantic memory is intact, and this particularly helps to differentiate from the semantic variant in early disease (Gorno-Tempini *et al.* 2011). Patients report word-finding difficulties and do display anomia, but the anomia is less severe than svPPA cases. Speech agrammatism manifests as use of short, simple phrases which can sound muddled and 'telegraphic', because of omission of short connecting words and other function words, use of words in the wrong order and misuse of word endings, verb tenses, pronouns, prepositions and conjunctions (Mesulam

2003; Rohrer *et al.* 2008). There is also difficulty in comprehending grammar, leading to impaired sentence comprehension, particularly if sentences are long and syntactically complex (Grossman and Moore 2005). Patients can develop binary word reversals (typically yes/no, or pronouns, e.g., he/she) saying the opposite word to what they intended (Frattali *et al.* 2003) or utter sudden, unintended, stereotyped responses such as ‘don’t know’ to different questions before giving the correct answer (Snowden and Neary 1993).

Speech apraxia impairs the patient’s ability to programme and plan the motor aspects of speech production properly, leading to effortful trial and error ‘groping’ of orofacial movements in the effort to produce the correct sounds (Duffy 2006; Josephs *et al.* 2006). Some patients perseverate on consonants or syllables, leading to a new ‘stuttering’ quality to speech as the initial presenting symptom (Kertesz *et al.* 2003). The variability in an apraxia of speech can lead to a misdiagnosis of a ‘functional stutter’ or functional speech disorder, i.e., of a non-organic basis by non-specialists, particularly as symptoms can fluctuate and become worse with anxiety or effort. The prosody of speech is also disrupted, thereby affecting its natural rhythm, rate (commonly leading to slowing), volume, or intonation (Josephs *et al.* 2006). There are typically distorted speech sounds (phonetic errors) because of errors in execution of programmed speech sounds, typified by syllable or consonant deletions, insertions, substitutions, distortions, repetitions and prolongations such as ‘capitain’ rather than ‘captain’ (Duffy 2006; Gorno-Tempini *et al.* 2011), which can all make speech sound ‘jumbled up’ to the patient and their relatives. Writing can be intact or show grammatical errors later on in disease.

With these core speech production features, the agrammatism affects language in a broader sense. Repetition of single words is relatively preserved (except for more complex multi-syllabic words which becomes effortful), but repetition of longer sentences that are grammatically complex is affected. Over time speech deteriorates to a point where the patient has extreme difficulty making them understood and eventually mutism ensues, while this can be an early feature in some cases (Gorno-Tempini *et al.* 2006). Many patients switch to non-oral methods of communication such as writing on a notepad, or electronic language applications on handheld tablet computers. Orofacial/buccofacial apraxia, is also seen, which impairs the patient’s ability to plan oral movements, leading to difficulty initiating swallowing, coughing and yawning (Tyrrell *et al.* 1991). On bedside testing, patients are unable to perform these actions to command, usually responding by repeating the word ‘cough’ or ‘yawn’ rather than the action itself (Tyrrell *et al.* 1991). Many patients display limb apraxia, particularly affecting the right side. Although subtle initially, this often worsens, progressively impairing hand function (Mesulam 2003).

LvPPA

Around 30% of patients with PPA have the more recently described syndrome lvPPA (Kertesz *et al.* 2003; Gorno-Tempini *et al.* 2004, 2008; Rosen *et al.* 2006). The hallmark imaging feature is left posterior temporoparietal atrophy encompassing the posterior superior temporal lobe, inferior parietal lobe, precuneus and mesial temporal lobe (Gorno-Tempini *et al.* 2004; Rohrer *et al.* 2013a). The syndrome is thought by some to be an atypical and unihemispheric presentation of AD (Ahmed *et al.* 2012; Rohrer *et al.* 2012), although associated pathology is not universally ‘AD-like’ (Harris *et al.* 2013a; Mesulam *et al.* 2014) and it is difficult to predict based on clinical features which patients have underlying AD versus other pathology (Chare *et al.* 2014). The key clinical features of lvPPA are frequent word-finding pauses, anomia and impaired sentence (rather than single word) repetition (Gorno-Tempini *et al.* 2004, 2008). There is also preserved single word comprehension and object knowledge as semantic memory is intact, but impaired comprehension of longer sentences, without agrammatism or apraxia of speech (Gorno-Tempini *et al.* 2008; Rohrer *et al.* 2012). On speech assessment, there are frequent pauses (as the patient tries to retrieve the right word rather than apraxia of speech), and phonological errors (which are well articulated and not distorted, but definitely incorrect, such as ‘coptain’ rather than ‘captain’) due to difficulty with the phonology of the anticipated word. These phonological errors also appear in writing, and there may be a phonological dyslexia, affecting reading of new or non-sense words. The short-term, phonological memory deficit in lvPPA also characteristically impairs sentence repetition in a length-dependent manner, but spares single word repetition (Gorno-Tempini *et al.* 2008). Although comprehension of single words is intact, there can be difficulty in comprehending longer sentences, because of the deficit in phonological memory, but this is not affected by grammatical complexity like in nfvPPA. Patients with severe lvPPA can be difficult to differentiate from patients with non-fluent PPA. However, the key differentiating features for lvPPA are lack of agrammatism, lack of apraxia speech, lack of orofacial apraxia, preserved prosody and impaired sentence repetition (Gorno-Tempini *et al.* 2008; Chare *et al.* 2014). Limb apraxia is often present due to parietal involvement (Rohrer *et al.* 2012).

Parkinsonism and motor features in PPA

Subtle signs of parkinsonism are observed in a large proportion of patients with PPA, mostly in patients with nfvPPA. Typically this is on the right-hand side (i.e. contralateral to predominant left hemispheric involvement) and leads to mild cogwheeling, bradykinesia or rigidity on examination when the other hand is engaged in repetitive and simultaneous tapping or subtle dystonia or asymmetrical posturing of the hand when distracted (Mesulam 2013).

As disease progresses, parkinsonism can worsen and lead to a frank parkinsonian syndrome, most commonly with features of CBS (Graham *et al.* 2003; Josephs *et al.* 2006; Josephs and Duffy 2008) and less commonly PSPS (Josephs *et al.* 2005, 2006). Overlap of svPPA with PSPS or CBS is rare, and if present, is usually associated with atypical FTLDTau pathology (Clerc *et al.* 2013), although parkinsonism can appear late on in disease (Hodges and Patterson 2007; Kremen *et al.* 2011). Patients with lvPPA typically do not develop florid parkinsonism (unless there is underlying CBD (corticobasal degeneration) pathology).

Similar to the bvFTD/MND spectrum, there are also patients with PPA that develop MND or clinical features suggestive of MND, but not fully meeting criteria, for example, mild wasting or fasciculations were seen in a small proportion of patients with nvPPA in one study (Burrell *et al.* 2011). Although most cases of PPA-MND have nvPPA; there is a subgroup of patients with RTLA who can rarely develop MND, typically associated with FTLDTDP type B pathology and predominant lower motor neuron features (Coon *et al.* 2012), or prominent upper motor neuron signs and pathological evidence of corticospinal tract degeneration and FTLDTDP type C pathology (Josephs *et al.* 2013). MND in typical svPPA and lvPPA is rare. Some MND patients develop language impairment not fully meeting criteria for PPA. Detection of aphasia in the presence of dysarthria can be difficult, however, so it may be under-reported; one recent study suggested language dysfunction in 43% of MND patients (Taylor *et al.* 2012). This needs further study, as these language difficulties will affect use of alternative communication methods such as electronic writing boards in patients who have lost motor speech because of bulbar involvement.

Clinical syndromes of familial FTD

Familial FTD is observed in around a third of all FTD cases, and more commonly presents as bvFTD than other FTD subtypes. Mutations in *MAPT*, *GRN* and *C9ORF72* are the most commonly identified causes of familial FTD, and in this section we summarize the clinical syndromes observed in these cases. We also describe the phenotype of patients with pathogenic mutations in rarer genes (*VCP*, *CHMP2B*, *TREM2*, *TARDBP*, *FUS*, *UBQLN2* and *SQSTM1*) and provide an overview of clinical syndromes recently discovered to be associated with mutations in the gene TRAF family member-associated NF-kappa-B activator (TANK)-binding kinase 1 (*TBK1*). A summary of the various features of the clinical syndromes associated with these genes is presented in Table 3.

MAPT

To date, there have been 55 pathogenic mutations identified in *MAPT*. Mean age at onset is in the mid-50s (Snowden

et al. 2015), with a peak age at onset between 45 and 65 years. On average, patients present younger than those with *GRN* or *C9ORF72* mutations, with an age at onset of < 50 years in around 50% of cases (Snowden *et al.* 2015). However, patients with *MAPT* mutations may have a broad range at onset from their 20s to their 80s (van Swieten and Spillantini 2007). Mean disease duration is 8 years (Snowden *et al.* 2015), but with a wide range of 5–30 years (Seelaar *et al.* 2011).

The typical clinical picture in *MAPT*-associated FTD is bvFTD with or without parkinsonism, with or without a degree of language decline (usually mild semantic impairment) later on in disease (Seelaar *et al.* 2011; Benussi *et al.* 2015). However, patients can present with a wide range of features, and there is generally poor correlation of clinical features with the underlying gene mutation (Benussi *et al.* 2015).

Parkinsonism can occasionally be the sole presenting feature of disease, but more typically develops after onset of bvFTD (van Swieten and Spillantini 2007; Kertesz *et al.* 2011; Rohrer and Warren 2011). Parkinsonism usually manifests as bradykinesia, rigidity (limb and/or axial), postural instability and poor response to levodopa (Park and Chung 2013; Siuda *et al.* 2014). However, a levodopa-responsive asymmetrical resting tremor has been observed in some patients (Tsuboi *et al.* 2002), although response is rarely sustained. Parkinsonism can be part of an isolated CBS (Rossi *et al.* 2008; Kouri *et al.* 2014) or less frequently PSPS (Rohrer *et al.* 2011b). Pyramidal signs, postural tremor, myoclonus, dystonia, dysarthria and abnormal eye movements have also been observed (Siuda *et al.* 2014). MND is rare, but lower motor neuron signs such as muscle wasting and fasciculations have also been reported (Zarranz *et al.* 2005; Di Fonzo *et al.* 2014).

Prominent behavioural features in patients with *MAPT* mutations include disinhibition, obsessionality and stereotyped repetitive behaviours, but apathy is less common than in *GRN* or *C9ORF72* cases (van Swieten and Spillantini 2007; Snowden *et al.* 2015). Executive dysfunction is well recognized in *MAPT* cases, but does not differentiate from patients with *GRN* or *C9ORF72* mutations (Snowden *et al.* 2015). Neuropsychiatric presentations are less common than in cases with *GRN* or *C9ORF72* mutations, but are still seen: a patient with the S356T mutation who had been diagnosed as schizophrenia aged 27 years had confirmed FTLDTau at post-mortem and a family history of 'schizophrenia' in her father, who died aged 42 years (Momeni *et al.* 2010b). Semantic impairment and anomia are common later in disease (Pickering-Brown *et al.* 2008; Rohrer *et al.* 2009a), and more common than in *GRN* cases (Snowden *et al.* 2015). Although a PPA presentation is much less common than in patients with *GRN* mutations (Pickering-Brown *et al.* 2008), a few patients have been described, for example, with nvPPA associated with V363I (Munoz *et al.* 2007; Rossi

Table 3 Summary of clinical features of familial frontotemporal dementia (FTD) syndromes

FTD gene	Age at onset (years)	Disease duration (years)	Typical clinical presentation	Prominent behavioural and psychiatric features	Language impairment	Other cognitive deficits	Parkinsonism/extrapyramidal features	Motor neuron features
MAPT	Mean: mid-50s Range: 20-80s	Mean: 8 Range: 5-30	BvFTD ± parkinsonism ± mild late language impairment	Disinhibition, obsessiveness, stereotyped repetitive behaviour; less apathy Psychiatric symptoms less common	Usually late semantic impairment and anomia; typical PPA presentation much less common	Episodic memory impairment in some cases	Common early on; usually limb/axial rigidity, bradykinesia, and tremor; poorly responsive to levodopa Can have frank PSPS/CBS	Rare
GRN	Mean: 59-65 Range: 35-89	Mean: 9 Range: 3-22	Variable; typically bvFTD>PPA >CBS. Can mimic AD	Apathy and social withdrawal Psychiatric common: delusions, hallucinations, obsessiveness, rituals	Common; either bvFTD with prominent early language impairment or frank PPA (e.g. nfvPPA or atypical presentation with PPA-U)	Episodic memory impairment, apraxia, dyscalculia, visuospatial dysfunction (parietal)	Common later on (found in 40-60%); asymmetrical parkinsonism with poor levodopa response, or CBS-like (limb apraxia and dystonia)	Rare
C9ORF72	Mean: 50 Range: 21-83	Mean 8-9 Range: 1-22	Typically bvFTD ± MND or MND alone; less commonly nfvPPA	Apathy, disinhibition, less sweet tooth, more complex unusual repetitive behaviours Psychosis and anxiety very common: odd delusions or auditory/tactile hallucinations; may mimic bipolar or schizophrenia	Less common, few have nfvPPA/svPPA	Early episodic memory impairment Profound executive dysfunction, impaired verbal and visual episodic memory, anomia, apraxia and dyscalculia	Common in bvFTD>PPA cases Typically ALS (bulbar onset in >40%); PLS and PMA rare	
TBK1	Mean: 65.5-72 Range: 48-80	Mean 7.1 Range 2-13	FTD-MND or MND alone > FTD alone Usually bvFTD, some cases of PPA	Disinhibition, aggression, motor agitation, apathy Psychiatric diagnoses common: bipolar disorder, schizophrenia, alcoholism, depression	bvFTD: word retrieval difficulties, reduced spontaneous speech PPA: reduced speech output, repetition difficulties, semantic paraphasias or nfvPPA with agrammatism	Early prominent episodic memory impairment	Very common; rigidity, postural or resting tremor, bradykinesia	Common; often with FTD but also MND alone Typically ALS with prominent upper motor neuron signs
VCP	FTD Mean: 57 Range: 49-60 Myopathy Mean: 42 Range: 24-61 Mean: 58 Range: 46-65	Death in 40-60s	Progressive myopathy, Page's disease, FTD in 30%	Apathy and disinhibition; psychotic features seen rarely	Aphasia and early semantic impairment common	Episodic memory impairment in a few cases	Rare, but can have late stage akinetic-rigid syndrome or early typical parkinsonism in some cases	Rare, usually myopathy or IBM-like, but can have MND
CHMP2B	Mean: 10 Range: 46-65	Mean: 10 Range: 46-65	Usually bvFTD; rare; mainly in single Danish family	Insidious onset of early behavioural change	Dynamic aphasia	Limited information available	Prominent late stage; asymmetrical akinetic-rigid syndrome, dystonia, myoclonus	Rare, can be PMA

(continued)

Table 3. (continued)

FTD gene	Age at onset (years)	Disease duration (years)	Typical clinical presentation	Prominent behavioural and psychiatric features	Language impairment	Other cognitive deficits	Parkinsonism/extrapyramidal features	Motor neuron features
TARDBP	Range: 29–77	Limited information available	Rare in FTD alone, more common in FTD-MND or MND alone	Variable, usually bvFTD/svPPA	Prominent semantic impairment in a few cases	Limited information available	Parkinsonism (including PSPS) seen in combination with MND	FTD-MND and MND much more common than FTD
SQSTM1	Mean: 60 Range: 48–73	Mean 10.2 Range 2–29	Rare in FTD alone, more common in FTD-MND or MND alone; can have concurrent Paget's disease of bone	BvFTD-like; some are atypical, e.g., right temporal FTD with semantic impairment, or CBS-like	Limited information available	Limited information available	Limited information available	FTD-MND and MND much more common than FTD
FUS	Mean: 40s to 50s	Mean 2–4	Rare in FTD alone, more common in MND alone, or FTD-MND	BvFTD-like	Limited information available	Limited information available	Limited information available	MND much more common than FTD
UBQLN2	Mean 40.6 Range: 16–71	Mean 3.8	Adult ALS-FTD or juvenile X-linked ALS; may appear sporadic	BvFTD-like, sometimes prior to motor symptoms	Limited information available	Limited information available	Limited information available	FTD-MND and MND much more common than FTD; limb/bulbar onset ALS
TREM2	Nasu-Hakola disease: 30s FTD-like syndrome: 30–40s	Death in 50 s	Homozygous mutations cause Nasu-Hakola disease, or FTD-like syndrome without bony involvement. Heterozygous variants associated with AD	Nasu-Hakola disease causes bony cysts, ankle swelling and fractures FTD-like syndrome with compound heterozygous mutations is bvFTD-like; seizures and visual hallucinations also observed	Present, including non-fluency, anomia, semantic paraphasias	Episodic memory and parietal impairment observed	Common; bradykinesia, postural instability	Brisk tendon reflexes seen

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; bvFTD, behavioural variant FTD; CBS, corticobasal syndrome; MND, motor neuron disease; ntVPPA, non-fluent variant primary progressive aphasia; PMA, progressive muscular atrophy; PPA-U, primary progressive aphasia unclassified; PSPS, progressive supranuclear palsy syndrome; svPPA, semantic variant primary progressive aphasia. Clinical features are adapted from tables in: Rohrer and Warren (2011) and Ng *et al.* (2015).

et al. 2014) and G304S (Villa *et al.* 2011) mutations and svPPA associated with V363I (Bessi *et al.* 2010) and P301L (Ishizuka *et al.* 2011) mutations. A novel mutation (C291R) has also been recently identified in a patient with PPA-CBS who had a prominent apraxia of speech (Marshall *et al.* 2015). Episodic memory loss can be prominent in some cases and has been found in association with profound hippocampal atrophy in patients with a R406W mutation (Tolboom *et al.* 2010), mimicking (and therefore mistakenly diagnosed as) early onset familial AD.

GRN

There are currently 82 pathogenic mutations described in *GRN*. Mean age at onset is later than *MAPT*, between 59 and 65 years, with a range of 35–89 years (Gass *et al.* 2006; van Swieten and Heutink 2008; Le Ber 2013), but this can vary widely even within the same family. A polymorphism in the *TMEM106B* gene has been shown to affect age at onset in *GRN* mutation carriers (Cruchaga *et al.* 2011; Finch *et al.* 2011; van der Zee *et al.* 2011). Disease duration is similar to *MAPT*, with a mean of 9 years (Snowden *et al.* 2015) and ranges from 3 to 22 years (Beck *et al.* 2008).

The clinical picture is variable and the identified mutation correlates poorly with the clinical syndrome. The most common presentation is bvFTD and less commonly PPA (Beck *et al.* 2008; Le Ber *et al.* 2008) and these two syndromes can occur within the same family. Cases with *GRN*-associated bvFTD can have a range of features as seen in sporadic bvFTD, but tend to have prominent apathy (Beck *et al.* 2008; Snowden *et al.* 2015) and social withdrawal. Between 10% and 30% of patients can present with episodic memory impairment (Le Ber *et al.* 2008), and when combined with evidence of apraxia, dyscalculia and visuospatial dysfunction secondary to early parietal atrophy, this may appear similar to AD. Neuropsychiatric manifestations are quite common, with patients displaying delusions, hallucinations or ritualistic and obsessive behaviours (Le Ber *et al.* 2008; Momeni *et al.* 2010a). In contrast to *MAPT* and *C9ORF72* cases, there is often predominant early language involvement or a language-only presentation. Around 10% of cases present with PPA, which can occasionally precede development of CBS (Baker *et al.* 2006; Cruts *et al.* 2006). Although the phenotype of speech disturbance is often described as nfvPPA, patients can often have widespread language dysfunction with features that do not neatly fit into one of the three main PPA phenotypes, more commonly fitting in to the PPA-not otherwise specified group (Rohrer *et al.* 2010a). Patients with PPA that appears 'mixed' or hard to classify, should therefore be investigated for the presence of a family history, or other supportive clinical or imaging features of a *GRN* mutation.

Extrapyramidal features are present in around 40–60% of cases with a *GRN* mutation, either just as asymmetrical parkinsonism or as a typical CBS-like presentation with limb

apraxia and dystonia (Kelley *et al.* 2009; Siuda *et al.* 2014). Unlike in *MAPT* cases, parkinsonism is not often an early feature, becoming evident well after bvFTD develops (Kelley *et al.* 2009). Parkinsonism does not usually improve with levodopa (Di Fabio *et al.* 2010), but can occasionally have an initial response.

MND is rarely seen, although in one large study, features of MND were found in 5.4% of patients with a *GRN* mutation (Chen-Plotkin *et al.* 2011).

C9ORF72

In 2011, two groups identified a hexanucleotide repeat expansion mutation in a non-coding region of the *C9ORF72* gene (DeJesus-Hernandez *et al.* 2011; Renton *et al.* 2011). Healthy individuals without the mutation usually carry 2–20 repeats on each allele. The number of repeats in mutation carriers is difficult to size accurately as it is so large, but most studies suggest patients usually possess 400–4400 repeats (Beck *et al.* 2013), with most possessing thousands. Although the minimum repeat number for disease is not clear, most consider > 30 repeats pathogenic (Simon-Sanchez *et al.* 2012; Beck *et al.* 2013; Woollacott and Mead 2014). The age at onset is extremely variable, ranging from 21 to 83 (mean 50) years (Hsiung *et al.* 2012; Majounie *et al.* 2012; Snowden *et al.* 2012). Similarly to cases with *GRN* mutations, a *TMEM106B* variant may also modify age at onset in *C9ORF72* expansion carriers (van Blitterswijk *et al.* 2014; Gallagher *et al.* 2014). Disease duration is highly variable, ranging from 1 to 22 years, with a mean of 8–9 years (Hsiung *et al.* 2012; Mahoney *et al.* 2012). Some studies have observed more rapid progression in patients with *C9ORF72*-associated FTD or MND, although slowly progressive FTD cases have been observed who survive for 15–20 years (Khan *et al.* 2012; Gomez-Tortosa *et al.* 2014; Suhonen *et al.* 2014), perhaps accounting for some cases previously thought to be bvFTD phenocopies (Rohrer *et al.* 2015a).

The typical presentation in *C9ORF72* expansion carriers is bvFTD, MND or a combination of FTD and MND. Prominent behavioural features include apathy, disinhibition and loss of empathy (Mahoney *et al.* 2012), while one study observed more emotional warmth in patients with bvFTD secondary to *C9ORF72* expansions than because of *MAPT* or *GRN* mutations (Snowden *et al.* 2015). Although many *C9ORF72* bvFTD patients have food fads or overeating, patients appear to have a relatively absent sweet tooth compared with non-*C9ORF72*-associated FTD cases (Snowden *et al.* 2012). Complex, unusual, repetitive or stereotyped behaviours are common: 59% of patients in one study displayed complex behavioural routines involving sorting, washing hands or cleaning (Snowden *et al.* 2012).

Language decline appears to be rarer than in patients with *GRN* and *MAPT* mutations; although *C9ORF72* expansions have been identified infrequently in PPA cases, including

fvPPA (Renton *et al.* 2011; Hsiung *et al.* 2012; Mahoney *et al.* 2012; Snowden *et al.* 2012) and svPPA (Renton *et al.* 2011; Snowden *et al.* 2012; Cerami *et al.* 2013; Josephs *et al.* 2013), these have not been described in detail and the PPA phenotype of *C9ORF72* expansion cases remains unclear.

On neuropsychological assessment, the key findings are profound executive dysfunction, reduced spontaneous/propositional speech, echolalia, perseveration, impaired verbal and visual episodic memory, anomia and dominant parietal deficits, particularly apraxia and dyscalculia (Mahoney *et al.* 2012; Snowden *et al.* 2012). Similarly to *MAPT* and *GRN* mutation-associated FTD, memory impairment can be a prominent and early feature (Mahoney *et al.* 2012), as can anxiety, which can lead to misdiagnosis of 'early onset AD'. An amnesic presentation has been observed in several large cohort studies of *C9ORF72* expansion carriers (Dobson-Stone *et al.* 2012; Mahoney *et al.* 2012), perhaps because of involvement of the parietal lobes and posterior cingulate gyrus (Irish *et al.* 2013). Patients presenting with prominent episodic memory impairment also have a later age at onset than those with *C9ORF72*-associated bvFTD (Wojtas *et al.* 2012; Cacace *et al.* 2013), which makes patients look even more similar to AD. In one study 2.6% of patients initially diagnosed with sporadic or familial AD possessed *C9ORF72* expansions; confusingly all had AD-like biomarkers in cerebrospinal fluid (although without histopathological confirmation), which further complicated the diagnostic picture (Wallon *et al.* 2012).

Psychiatric presentations are common, particularly psychosis (Arighi *et al.* 2012; Boeve *et al.* 2012; Calvo *et al.* 2012; Dobson-Stone *et al.* 2012; Englund *et al.* 2012; Mahoney *et al.* 2012; Galimberti *et al.* 2013; Kertesz *et al.* 2013; Devenney *et al.* 2014; Snowden *et al.* 2015). Typical features include delusions, visual or auditory hallucinations, odd somatoform or tactile hallucinations and prominent agitation and anxiety, perhaps due to altered body schema processing associated with cortico-thalamo-cerebellar network involvement (Downey *et al.* 2014). Bipolar disorder and obsessive-compulsive-like presentations are also seen: in a study of 32 patients with FTD or FTD-MND and the *C9ORF72* expansion, 38% had prominent psychotic features at presentation and had been diagnosed with paranoid schizophrenia, delusional psychosis or a somatoform psychosis (Snowden *et al.* 2012). However, cases with a *C9ORF72* expansion have been only very rarely identified in individuals with typical schizophrenia (0.67%) (Galimberti *et al.* 2014a) or bipolar disorder (0.5–1%) (Meisler *et al.* 2013; Galimberti *et al.* 2014b).

Parkinsonism is also common and in some studies detectable in up to a third of patients (Boeve *et al.* 2012). It typically manifests as a symmetrical akinetic-rigid syndrome with gait disturbance, with or without a tremor that is usually postural or action, but rarely resting, in nature.

Occasionally, parkinsonism can be the sole manifestation for over 10 years, only later morphing into more typical bvFTD. Most patients do not benefit from levodopa. The expansion has also been detected in a few patients who have been clinically diagnosed with another neurodegenerative disorder including idiopathic Parkinson's disease, (O'Dowd *et al.* 2012; Cooper-Knock *et al.* 2013; Lesage *et al.* 2013), Lewy body dementia (Robinson *et al.* 2014), multiple system atrophy (Goldman *et al.* 2014), PSPS (Origone *et al.* 2013), CBS (Lindquist *et al.* 2013), prion disease (Majounie *et al.* 2012; Beck *et al.* 2013) and Huntington's disease phenocopies (Hensman Moss *et al.* 2014). There have been a small number of cases with prominent (Lindquist *et al.* 2013) or isolated (Corcia *et al.* 2015) cerebellar ataxia associated with the *C9ORF72* expansion.

All subtypes of MND have been observed in association with the expansion, although adult-onset ALS is by far the most common and often indistinguishable from sporadic ALS (Cooper-Knock *et al.* 2012; Snowden *et al.* 2013). Patients with *C9ORF72*-associated MND tend to have a higher prevalence of behavioural changes and cognitive impairment (Millecamps *et al.* 2012; Montuschi *et al.* 2015).

VCP

In 2004, mutations in *VCP* on chromosome 9p13.3 were identified in cases of inclusion body myositis with Paget's disease of the bone and FTD, an autosomal dominant 'multisystem proteinopathy' (Watts *et al.* 2004; Benatar *et al.* 2013). *VCP* mutations have very rarely been described as causing isolated FTD (van der Zee *et al.* 2009). Although at least 19 mutations exist they account for < 1% of cases of FTD overall (Cruts *et al.* 2012). The clinical presentation tends to start with a myopathy in the fourth decade in 90% of cases, with subsequent cognitive decline from the fifth decade onwards in 30% of patients and Paget's disease in 45%. Most patients develop bvFTD, although early semantic and other language deficits are also observed (Kim *et al.* 2011), and an MND phenotype, with or without FTD overlap (Miller *et al.* 2012; Hirano *et al.* 2015) is seen more rarely. Although parkinsonism is rare, several mutations are associated with development of an akinetic-rigid syndrome in later disease stages (Watts *et al.* 2004; van der Zee *et al.* 2009; Spina *et al.* 2013), and rare cases present as idiopathic Parkinson's disease with levodopa responsiveness (Chan *et al.* 2012).

CHMP2B

Study of a large Danish kindred with familial FTD (Skibinski *et al.* 2005) led to the discovery of the *CHMP2B* gene mutation on chromosome 3p11.2. Outside of this family, variants in *CHMP2B* have been identified only extremely rarely. Most cases have FTLD-UPS, characterized by inclusions that are positive for ubiquitin and p62, but

negative for TDP-43 and FUS on histopathological analysis of brain tissue (Holm *et al.* 2009). Average age at onset of FTD is 58 (range 46–65) years, with average disease duration of around 10 years, although disease often presents insidiously and can be slowly progressive. The typical clinical presentation is bvFTD, often with more widespread cognitive impairment, combined with prominent late parkinsonism (usually an asymmetrical akinetic-rigid syndrome), dystonia, pyramidal signs and myoclonus (Gydesen *et al.* 2002; Stokholm *et al.* 2013). MND has been reported in a few cases (Parkinson *et al.* 2006; Cox *et al.* 2010).

TARDBP

Mutations in the *TARDBP* gene on chromosome 1 were initially identified in familial and sporadic ALS cases (Kabashi *et al.* 2008; Rutherford *et al.* 2008; Sreedharan *et al.* 2008; Van Deerlin *et al.* 2008), and account for 4–6% of familial ALS cases and 1% of sporadic ALS cases. They also account for a small proportion of cases with combined FTD-MND (Benajiba *et al.* 2009; Chio *et al.* 2010), associated with a broad phenotype including features of parkinsonism or an overlap syndrome of MND/PSPS (Moreno *et al.* 2015). One case of bvFTD with a supranuclear gaze palsy and chorea has been observed (Kovacs *et al.* 2009). *TARDBP* mutations are very rare in pure FTD, with < 20 cases currently identified; even fewer have had neuropathological confirmation of FTLN (Gitcho *et al.* 2009; Gelpi *et al.* 2014; Moreno *et al.* 2015). FTD cases have had bvFTD or svPPA, with a wide range of age at onset (29–77 years) (Borroni *et al.* 2009; Gitcho *et al.* 2009; Gelpi *et al.* 2014; Synofzik *et al.* 2014; Moreno *et al.* 2015).

SQSTM1

Mutations in *SQSTM1* (encoding for p62/sequestome 1) on chromosome 5q35 lead to isolated Paget's disease of the bone (Gennari *et al.* 2010), which is a clinical feature also found in cases of multisystem proteinopathy associated with *VCP-1* mutations. More recently, *SQSTM1* mutations have also been identified in familial and sporadic MND and FTD-MND (Fecto *et al.* 2011; Rubino *et al.* 2012; Chen *et al.* 2014). However, they have recently been identified in a small number of patients with pure FTD without associated ALS (Le Ber *et al.* 2013; Miller *et al.* 2015). The clinical phenotype of FTD with underlying *SQSTM1* mutations appears to be highly variable. The average age at onset is 60 years (range 48–73), with an average disease duration of 10 years (range 2–29) (Le Ber *et al.* 2013). The majority of patients present with a bvFTD-like syndrome, with a third having concurrent Paget's disease of the bone. In a more recent case series of 465 FTLN patients, four patients had *SQSTM1* mutations (0.85%), all of whom presented with atypical FTD syndromes including bvFTD, RTLA with prominent semantic impairment and CBS (Miller *et al.* 2015).

FUS

Similarly to *TARDBP*, *FUS* mutations are far more prevalent in familial ALS (4%) and sporadic ALS (< 1%) than in FTD-MND or FTD alone (Ng *et al.* 2015). The first ALS-associated mutation in *FUS* on chromosome 16p11.2 was identified in 2009 (Kwiatkowski *et al.* 2009; Vance *et al.* 2009), and was associated with characteristic FUS-positive protein inclusions in spinal cord neurons. However, *FUS* mutations are rarely seen in patients with FTD who have this pathology in brain tissue. Currently four mutations linked to FTD-MND exist (Ticozzi *et al.* 2009; Blair *et al.* 2010; Broustal *et al.* 2010; Yan *et al.* 2010) and two cases of pure bvFTD with a *FUS* variant have been reported (Van Langenhove *et al.* 2010; Huey *et al.* 2012).

UBQLN2

Originally identified in association with X-linked familial ALS, four further mutations in *UBQLN2* were identified in a study of another 40 patients with MND with an apparently X-linked mode of transmission (Deng *et al.* 2011). Twenty-three per cent of these patients had FTD-MND, usually with a bvFTD phenotype which occasionally preceded onset of motor symptoms, and age at onset varied widely (16–71 years) with a disease duration usually < 4 years. A more recent study found *UBQLN2* mutations in 2/161 ALS patients and 1/45 FTD patients, with all patients presenting with apparently sporadic disease (Synofzik *et al.* 2012).

TREM2

Mutations in the gene *TREM2* on chromosome 6p21.1 were first identified in association with an autosomal recessive, rare condition called polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOS or Nasu-Hakola disease) (Paloneva *et al.* 2000). Patients with Nasu-Hakola disease develop multifocal bony cysts, ankle swelling and fractures in the third decade, followed by an FTD-like cognitive decline in the fourth decade and death in the fifth decade. More recently there have been observations of patients with homozygous or compound heterozygous *TREM2* mutations who develop dementia without bony involvement (Chouery *et al.* 2008; Giraldo *et al.* 2013; Guerreiro *et al.* 2013a,c; Lattante *et al.* 2013; Rayaprolu *et al.* 2013; Le Ber *et al.* 2014). Patients developed cognitive and neuropsychiatric symptoms in their 30s to late 40s, characterized by a frontal dysexecutive syndrome, reduced empathy, disinhibition and overeating, as well as language dysfunction, episodic memory problems, parietal deficits, parkinsonism (mainly bradykinesia) and seizures. Death ensued by late 40s or 50s in most cases. Heterozygous *TREM2* variants have recently been described as a risk factor for AD (Benitez *et al.* 2013; Guerreiro *et al.* 2013b; Jonsson *et al.* 2013; Pottier *et al.* 2013), but studies have been mixed as to whether this is also the case for FTD (Lattante *et al.* 2013; Rayaprolu *et al.* 2013; Borroni *et al.* 2014; Cuyvers

et al. 2014; Ruiz *et al.* 2014; Slattery *et al.* 2014; Thelen *et al.* 2014; Lill *et al.* 2015).

TBK1

Mutations in the gene *TBK1* were recently identified in cohorts of MND, FTD and FTD-MND patients (Cirulli *et al.* 2015; Freischmidt *et al.* 2015; Gijssels *et al.* 2015; Le Ber *et al.* 2015; Pottier *et al.* 2015). The overall prevalence of *TBK1* mutations across the FTD and MND spectrum ranges from 0.4% to 4.5%, but mutations are more common in FTD-MND and rare in FTD alone. For example, one recent study identified a *TBK1* mutation in 0.5% of patients with isolated MND, but 10.8% of familial FTD-MND patients, although mutations were rare in isolated FTD (1 patient only) (Le Ber *et al.* 2015). In a Belgian study, loss-of-function mutations were identified in 1.1% (5/460) with isolated FTD, 3.4% (5/147) with isolated MND and 4.5% (1/22) with FTD-MND (Gijssels *et al.* 2015). Dual mutations seem to be common including concurrent *C9ORF72* expansions (Gijssels *et al.* 2015) and mutations in the optineurin (*OPTN*) (Pottier *et al.* 2015) or *FUS* (Freischmidt *et al.* 2015) genes. In one study of patients with confirmed FTLT-TDP and clinical FTD, age at onset of cognitive symptoms ranged from 64 to 80 years, with an average disease duration of 5.6 years (range 2–10 years) (Pottier *et al.* 2015). Clinical diagnoses of those presenting with dementia were heterogeneous, including bvFTD, nfvPPA, AD or FTD-ALS. In another study of seven patients with *TBK1* mutations and FTD (one with concurrent MND), the average age at onset was 66.3 years (Van Mossevelde *et al.* 2016): five out of six cases with isolated FTD had bvFTD but with early episodic memory impairment as well as prominent parkinsonism (Gijssels *et al.* 2015; Van Mossevelde *et al.* 2016), while the other case developed PPA aged 70 years with reduced speech output, word retrieval difficulties and semantic paraphasias (Van Mossevelde *et al.* 2016). NfvPPA with prominent agrammatism has also been described in a patient with combined *TBK1/OPTN* mutations Pottier *et al.* 2015). Similar to *C9ORF72* expansion carriers, a high proportion of MND cases with a *TBK1* mutation (~50% in one study) demonstrated cognitive impairment (Freischmidt *et al.* 2015). Further studies in larger cohorts with detailed clinical phenotyping and clinicopathological correlation will be invaluable to clarify the spectrum of *TBK1*-associated neurodegenerative disease and to inform clinicians about which patients they should test for these mutations.

Pre-symptomatic individuals

With an increasing number of gene mutations linked to FTD, and as potential treatments for FTD appear on the horizon, we need sensitive and reliable biomarkers of disease for use in clinical trials of patients with sporadic and familial FTD. In other diseases, such as AD and Huntington's disease, there is evidence of change in a number of biomarkers several

years prior to symptom onset (Scahill *et al.* 2002; Tabrizi *et al.* 2009; Bateman *et al.* 2012), suggesting that one needs to intervene well before clinical symptoms develop to significantly ameliorate disease. Up until now, large scale analyses of neuropsychological and neuroimaging biomarkers have been notably absent in both sporadic and familial FTD (Rohrer *et al.* 2013b), and there are no reliable fluid (blood, cerebrospinal fluid or urine) biomarkers of FTD itself, or of its underlying pathology, except for reduced serum and cerebrospinal fluid (CSF) progranulin levels in the majority of symptomatic patients and pre-symptomatic carriers of the *GRN* mutation (Carecchio *et al.* 2009; Finch *et al.* 2009). However, through monitoring families with FTD-associated gene mutations over many years, we will start to gain invaluable insights into these patterns and enable detection and validation of such biomarkers. Several studies have examined pre-symptomatic changes in individuals with familial FTD mutations, but most studies were on a case series basis. More recently, a large study of 220 individuals recruited from 11 research sites across Europe and Canada within the Genetic Frontotemporal Dementia Initiative demonstrated that cognitive and structural imaging changes can be detected 5–10 years before expected onset of symptoms (calculated from the mean familial age at onset) in adults at risk of familial FTD (Rohrer *et al.* 2015b). This study examined 118 mutation carriers (40 symptomatic: 11 with mutations in *MAPT*, 13 in *GRN* and 16 with the *C9ORF72* expansion), 78 pre-symptomatic mutation carriers (15 with *MAPT* mutations, 45 with *GRN* mutations and 18 with the *C9ORF72* expansion) and 102 individuals without the mutation ('non-carriers'). Carriers displayed deficits on neuropsychological assessment across a wide range of tests as early as 5 years before predicted symptom onset. Deficits were particularly pronounced on tests of naming and executive function. There were differences between groups in which test detected changes the earliest: the Boston Naming Test and the Cambridge Behavioral Inventory–Revised (CBI-R) version showed abnormalities earliest for *MAPT* mutation carriers, the backwards Digit Span for *GRN* mutation carriers and the CBI-R for *C9ORF72* expansion carriers. There also appeared to be an ordered series of neuroimaging changes across all mutation groups prior to expected onset of symptoms. Insular atrophy was evident on volumetric analysis of MRI brain scans of mutation carriers 10 years before expected onset of symptoms, followed by temporal lobe atrophy (also at 10 years before expected onset), then reduced frontal lobe, subcortical and whole brain volumes at 5 years before expected onset. There were also specific patterns of sequential atrophy within each group: *MAPT* mutation carriers first showed atrophy of the hippocampus and amygdala, *GRN* mutation carriers showed early insular atrophy (15 years prior to expected onset) and *C9ORF72* expansion carriers had very early subcortical (thalamic), insular, and posterior cortical atrophy (25 years

prior to expected onset). The long ‘run-in’ of changes prior to clinical onset of symptoms emphasizes the urgent need for identification and validation of other biomarkers of the disease process in familial and sporadic FTD, such as blood or CSF biomarkers, which can be measured over time.

Current challenges and future research

In a disease as complex as FTD, there are multiple challenges for the clinician and scientist. These are inherent in research studies aiming to improve our understanding of disease pathogenesis and disease presentation, identify novel treatments and implement better care for these patients and their families. However, in this section we have focused on summarizing challenges commonly encountered by clinicians managing patients with FTD and suggest future avenues for research in order to address these.

Diagnosis and prognosis of FTD syndromes

Making a correct and early diagnosis is essential for both the clinician and the patient with FTD, as it allows access to information about current and future symptoms, likely disease course and avoidance of unnecessary or inappropriate treatments. As discussed earlier, there are several features of the various FTD syndromes that are also seen in other neurodegenerative diseases such as AD or idiopathic Parkinson’s disease and in psychiatric disease. In PPA, it can also be difficult to differentiate between patients with lvPPA (around 70% of whom have AD pathology) and nvPPA (the majority of whom have FTLN pathology). Patients misdiagnosed as AD, Parkinson’s disease or an atypical psychiatric syndrome may be offered treatment with acetylcholinesterase inhibitors, levodopa preparations or antidepressant or anti-psychotic medications that are at best ineffective in FTD or at worst offer no benefit with significant and unnecessary side effects. In addition to guiding appropriate pharmacological treatments, a correct diagnosis allows appreciation of the support needed by patients with different features of FTD, for example, access to a specialist speech and language therapist for management of PPA, or a specialist nurse with detailed knowledge of common practical issues or symptoms that patients and their relatives with FTD face on a daily basis. There are also several national support groups for patients with FTD and their relatives, which can be invaluable for informal advice, support and social contact. The main barriers preventing correct and timely diagnosis of FTD are a lack of awareness about and understanding of the clinical and pathological overlap between a variety of neurodegenerative diseases, and the lack of available reliable biomarkers to differentiate between these. Some clinicians may not be aware that AD pathology can lead to a clinical presentation of FTD or AD, and that FTLN pathology can lead to symptoms of episodic memory loss in FTD, thus present like AD in a small

proportion of cases. In primary care, where FTD is rare, and AD is common, an AD diagnosis might have been made several years ago, before new symptoms prompt onward specialist referral and reconsideration of diagnosis. The use of CSF biomarkers of amyloid-beta and tau, and in some centres amyloid PET imaging, can be helpful in differentiating cases with underlying AD pathology. However, these types of biomarkers do not currently exist for FTLN pathology, and unless there is a known FTD-associated gene mutation, patients with FTD and prominent memory symptoms may still be diagnosed with AD even in the absence of definite biomarker evidence. Future research should elucidate biomarkers of FTD that could be used in combination with AD and markers of other neurodegenerative diseases to characterize these different syndromes more carefully.

As discussed earlier, many of the familial FTD syndromes also include parkinsonism or psychiatric phenomena either early on or at some point in the disease course. This may occur in the context of a strong family history of psychiatric disease (which in itself is also common) or with seemingly ‘unrelated’ cases of MND or dementia in the family (also common) or, if there is incomplete penetrance of a mutation, or a small family, a complete absence of family history. This clinical and familial heterogeneity makes it even more difficult to decide if a patient has sporadic or familial FTD, and research should focus on longitudinal phenotyping of large cohorts of patients with sporadic and familial FTD, with varying degrees of family history and clinical presentations, to expand our knowledge of what could be used to indicate genetic risk of disease. In the current absence of consistently reliable indicators of familial disease (other than a known gene mutation within the family), it may be prudent to consider offering genetic testing to all newly diagnosed (and previously diagnosed) patients with FTD, particularly bvFTD and FTD-MND.

Recent advances in diagnostic techniques in FTD, particularly neuroimaging, have enabled earlier and more accurate visual detection of FTD. There have also been significant improvements in recent understanding of the various patterns of atrophy across subtypes of sporadic and familial FTD. However, it is still difficult to categorize some patients clinically into which subtype of FTD they have, despite use of recently revised diagnostic criteria (Gorno-Tempini *et al.* 2011; Rascovsky *et al.* 2011). The key purpose of such precise clinical subtyping (particularly in patients with sporadic FTD) is to predict underlying pathology and hence target future treatments appropriately. This is also necessary to enable accurate advice about disease course, predicted survival and awareness of possible new symptoms or diseases (e.g. orofacial apraxia and dysphagia in nvPPA and risk of parkinsonism in FTD with *MAPT* mutations). A practical problem also arises in patients with overlap syndromes such as FTD-MND or PSPS-nvPPA. The increasing subspecialisation of neurologists, particularly in

tertiary centres, means that although patients get expert care for each aspect of their disease, they end up with multiple appointments with more than one specialist (cognitive, motor nerve and movement disorder). It is not clear which model of care is best. Should there be multidisciplinary clinics with experts from each FTD-associated syndrome present? These questions about best pathways for care and patient preference need addressing in future research.

Assessing disease severity and stage in FTD is important for guiding patient selection for inclusion in future clinical trials and for sensitive assessment of response to treatments in trials and in practice. Predicting disease onset and progression accurately is vital for advising patients and their relatives about prognosis, and for advising pre-symptomatic individuals who possess FTD-associated gene mutations when they are likely to develop symptoms. However, how best to assess disease severity is currently unclear: should it be through scores on neuropsychological batteries, impairment on functional rating scales, use of dementia staging scales currently available for use in AD, duration of symptoms or a combination of these? At present, clinicians are unable to provide reliable information to patients about how quickly their symptoms will progress, when they will lose specific functions and when they might develop new behavioural, language or motor changes. In practice, clinicians often tend to advise that the disease is likely to continue to progress at the previous rate of symptom progression seen in that patient so far, but this is rather non-specific and not all patients will develop all features of their disease phenotype. This makes planning for the future very difficult and this uncertainty is likely to have a significant psychological (and potentially financial) impact on patients, their carers and genetically at-risk relatives. If we were able to predict these milestones more accurately, this would allow appropriate and practical advanced decisions to be made about care and finances and timely introduction of currently available management strategies, such as alternative (non-oral) methods of communication.

Dilemmas in familial FTD

Several specific challenges remain for clinicians managing patients with familial FTD and their relatives, and future work should be directed towards addressing these. The first challenge is to be able to detect presence of disease well before the onset of symptoms and before significant atrophy is evident on neuroimaging, and in particular to understand the nature and timing of the series of changes that occur. This would enable us to predict more accurately when pre-symptomatic gene carriers will develop clinically relevant symptoms, intervene before this with timely treatment and monitor for response or progression over time. It will also inform families with mutations like the *C9ORF72* expansion, which have highly variable clinical features, age at onset and penetrance, about which individuals will develop symptoms,

which symptoms are likely and at what age these may start. This will allow better genetic counselling of 'at-risk' relatives of patients with familial FTD who might wish to pursue genetic testing, and useful advice for individuals who test positive for a gene mutation but are currently pre-symptomatic, about what lies ahead of them. In particular, even before successful treatments are developed, better knowledge about disease risk and likelihood of familial disease may encourage more individuals at risk to opt for pre-implantation genetic diagnosis, to reduce transmission of the gene mutation in successive generations. Greater awareness of the risk of familial disease within these syndromes is also needed across the spectrum of clinicians managing patients with FTD and MND, particularly for non-specialists who may feel that the absence of a family history precludes genetic risk. As the spectrum of neurodegenerative genes widens, there is an urgent need for production of comprehensive and regularly updated guidelines for clinicians managing patients with potentially familial diseases, and for greater public awareness of these conditions.

The second challenge is to understand why individuals with the same gene mutation develop either FTD or MND or both, and why some develop additional features such as parkinsonism or psychosis. If we understood this, it could elucidate the networks or pathways involved in pathogenesis of familial FTD, sporadic FTD and neurodegeneration in general.

Finally, we should use familial FTD as a paradigm (because of a relatively good link between typical pathology and underlying gene mutation) for clinicopathological study to clarify the complex pathological heterogeneity of FTLD and understand how this leads to various phenotypes of clinical disease. We need to be able to correlate histopathology with disease course and other biomarkers of FTD so we can be more certain that any future biomarkers used for disease detection, monitoring or categorization in life are associated with the actual pathology leading to disease. This may also enable translation of biomarkers identified in familial disease for use in individuals with sporadic FTD, whose pathology and clinical presentations remain even more complex and heterogeneous than in familial FTD. All of these avenues of research will be easier to pursue through collaborative studies of large cohorts of patients and pre-symptomatic individuals with familial FTD gene mutations, who undergo detailed phenotyping in a structured and homogeneous manner over time, such as within the Genetic Frontotemporal Dementia Initiative (Rohrer *et al.* 2015b).

In summary, we have made huge progress in recent years in understanding the clinical heterogeneity of FTD and how it relates to its underlying molecular cause, but there are still a number of challenges ahead for the field. As the focus of FTD research switches to the development of disease-modifying therapy and trials of such treatments, it will be important not to forget that the study of how to improve the

day-to-day care of symptomatic FTD patients, including finding better symptomatic medications, will need to remain a major research target.

Acknowledgments and conflict of interest disclosure

IOCW is funded by an MRC Clinical Research Training Fellowship. JDR is an MRC Clinician Scientist and has also received funding from the NIHR Rare Diseases Translational Research Collaboration.

The authors have no conflict of interest to declare.

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