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Behavioural Variant Frontotemporal Dementia—Defining Genetic and Pathological Subtypes

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Abstract Behavioural variant frontotemporal dementia (bvFTD) is a clinically, genetically and pathologically heterogeneous neurodegenerative disorder caused by FTLD-tau, FTLD-TDP and FTLD-FUS pathologies. Clinically, patients present with behavioural symptoms that may include one or more of disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative, stereotyped and compulsive/ritualistic behaviour or hyperorality/dietary changes. Cognitive deficits, particularly executive dysfunction, are also seen. Neuroanatomically, patients have frontal and/or temporal lobe atrophy on neuroimaging. However, there is currently no clear correlation between the clinical and neuroanatomical phenotype in life and the underlying pathogenetics. With the advent of clinical trials in bvFTD, establishing the underlying pathology accurately during life will become increasingly important. This review therefore investigates current and future biomarkers that may help make a pathological diagnosis in life, i.e. bvFTD-tau, bvFTD-TDP and bvFTD-FUS, including clinical and neuropsychological data, neuroimaging, blood and CSF markers.

Keywords Frontotemporal dementia · Frontotemporal lobar degeneration · Tau · TDP-43 · Progranulin · FUS

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Introduction

Behavioural variant frontotemporal dementia (bvFTD) is the second most common young-onset neurodegenerative dementia after Alzheimer's disease (Neary et al. 1998; Rascovsky et al. 2007; Cairns et al. 2007; Mackenzie et al. 2010; Seelaar et al. 2011). It forms part of the frontotemporal lobar degeneration (FTLD) spectrum of disorders, overlapping with the language disorders semantic dementia (SD) and progressive nonfluent aphasia, as well as the motor disorders corticobasal syndrome (CBS), progressive supranuclear palsy (PSP) and motor neurone disease (MND)/amyotrophic lateral sclerosis (ALS; Burrell and Hodges 2010; Seelaar et al. 2010, 2011; Piguet et al. 2011).

Clinically, bvFTD is characterized by progressive impairment of behaviour and change in personality (Neary et al. 1998; Rascovsky et al. 2011). In the revised International bvFTD Criteria Consortium criteria, these symptoms are grouped into five main clusters of abnormal behaviour: disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative, stereotyped and compulsive/ritualistic behaviour and hyperorality/dietary changes (Rascovsky et al. 2011; Table 1). As well as these behavioural features, a sixth item is included within the criteria, the typical neuropsychological profile of most patients with bvFTD: impaired executive function with relative sparing of memory and visuospatial functions. Clinical presentation is heterogeneous in bvFTD, and patients' first symptoms usually consist of one or more of these six behavioural and cognitive features. As the disease progresses, these symptoms change both in nature and severity. There have been some suggestions that there may be specific clinical subtypes within this heterogeneity (e.g. disinhibition-predominant, apathy-predominant and stereo-

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Table 1 Behavioural symptoms of bvFTD (adapted from International bvFTD Criteria, Rascovsky et al. 2011)

Main abnormal behaviour	Subtypes of abnormal behaviour	Examples
Disinhibition	Socially inappropriate behaviour	Inappropriately approaching, touching or kissing strangers, verbal or physical aggression, criminal behaviour, inappropriate sexual acts
	Loss of manners or decorum	Inappropriate laughter, jokes or opinions that may be offensive to others, lack of etiquette, loss of respect for personal space, poor hygiene or grooming, inappropriate physical behaviours
	Impulsive, rash or careless actions	Reckless driving, new-onset gambling, buying or selling objects without regard for consequences
Apathy/inertia	Apathy	Lacking initiative, ceasing to engage in activities or hobbies
	Inertia	Needs prompting to initiate or continue routine activities, less likely to initiate or sustain a conversation
Loss of sympathy/empathy	Diminished response to other people's needs and feelings	Making hurtful comments or disregarding other people's pain or distress
	Diminished social interest, interrelatedness or personal warmth	Decrease in social engagement, emotional detachment, distant from friends and relatives
Perseverative, stereotyped and compulsive/ritualistic behaviour	Simple repetitive movements	Tapping, clapping, rubbing, scratching, picking at skin or clothing, humming, rocking
	Complex, compulsive or ritualistic behaviours	Counting and cleaning rituals, collecting or hoarding, checking, ordering objects, walking fixed routes
	Stereotypy of speech	Habitual repetition of single words, phrases or themes
Hyperorality/dietary changes	Altered food preferences	Carbohydrate cravings (particularly sweets), food fads
	Binge eating, increased consumption of alcohol or cigarettes	Consuming excessive amounts of food, compulsive ingestion of alcohol or smoking
	Oral exploration or consumption of inedible objects	Pica, features of Kluver–Bucy syndrome

typed behaviour-predominant bvFTD (Snowden et al. 2002), but there have been no rigorous studies of this.

Neuroanatomically, bvFTD is characterised by frontal and/or temporal lobe atrophy, and this is now a supportive feature within the revised diagnostic criteria (Rascovsky et al. 2011). Although there is a certain amount of heterogeneity in the imaging features of different patients, one study has suggested via a cluster analysis that there are four distinct anatomical subtypes of bvFTD: frontal-dominant, temporal-dominant, frontotemporal and temporofrontoparietal (Whitwell et al. 2009b).

Genetically, up to 50% of cases with bvFTD will have a family history of the disease (Rohrer et al. 2009). Although six disease-causing genes have currently been associated with bvFTD (progranulin (*GRN*), microtubule-associated protein tau (*MAPT*), valosin-containing protein, chromatin-modifying protein 2B, transactive response DNA-binding protein and fused in sarcoma (*FUS*)), only two of these (*GRN* and *MAPT*) are major causes of bvFTD, each accounting for 5–10% of cases of bvFTD (Rohrer et al. 2009).

Pathologically, there are three major causes of bvFTD based on the abnormal protein found in neuronal inclusions—tau (FTLD-tau), TDP-43 (FTLD-TDP, which encompasses the majority of the tau-negative, ubiquitin-positive or FTLD-U cases) and FUS (FTLD-FUS, the minority of FTLD-U cases). Within each of these groups, there are a number of specific neuropathological subtypes: for tau, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Pick's disease (PiD), and the pathology associated with mutations in the *MAPT* gene can all cause bvFTD, as can all of the FTLD-TDP subtypes (types 1, 2, 3 and 4) and the FTLD-FUS subtypes (atypical FTLD with ubiquitin inclusions (aFTLD-U), neuronal intermediate filament inclusion disease (NIFID), and basophilic inclusion body disease (BIBD)) (Hodges et al. 2004; Knopman et al. 2005; Kertesz et al. 2005; Shi et al. 2005; Josephs et al. 2006; Snowden et al. 2007; Hu et al. 2007a, b; Lladó et al. 2008; Neumann et al. 2009; Munoz et al. 2009; Rohrer et al. 2010b, 2011). The frequency of these different pathological subtypes varies, however, with most large series (Table 2) showing that FTLD-tau is slightly less common than FTLD-U (FTLD-TDP or FTLD-FUS). Within FTLD-tau, most studies suggest that PiD is the most common subtype, although in geographical areas where *MAPT* mutations are common,

Table 2 Case series describing pathologically confirmed bvFTD cases

	FTLD-tau					FTLD-U	DLDH/Other
	PiD	MAPT	CBD	PSP	Other/NOS		
Hodges et al. 2004	11	0	0	0	3	2	10
Knopman et al. 2005	2	2	0	1	0	11	3
Kertesz et al. 2005	3	0	4	0	0	14	11
Shi et al. 2005	10	11	0	0	0	12	9
Josephs et al. 2006	9	0	2	2	1	21	3
Hu et al. 2007a, b	10	4	5	4	1	32	0
Lladó et al. 2008	3	3	2	0	2	3	4

PiD Pick's disease, MAPT pathology associated with MAPT mutations, *CBD* corticobasal degeneration, *PSP* progressive supranuclear palsy, *NOS* not otherwise specified, *DLDH* dementia lacking distinctive histology

the incidence is similar to PiD. CBD and PSP can both cause a bvFTD syndrome but are less common. In more recent studies (following the discovery of the TDP-43 and FUS proteins), it appears that type 1 FTLD-TDP (Sampathu classification) is only a rare cause of bvFTD (usually causing SD instead), with both type 2 and type 3 (including *GRN* mutations) both relatively common causes (with type 3 slightly more predominant than type 2) (Snowden et al. 2007; Rohrer et al. 2010b; Whitwell et al. 2010). FTLD-FUS appears to be a relatively rare cause of bvFTD (probably accounting for only 5–10% of cases), with aFTLD-U the most common subtype (Neumann et al. 2009; Rohrer et al. 2011; Urwin et al. 2010; Snowden et al. 2011). One final important point to make is that in a number of these series, a few cases of non-FTLD pathologies were reported, including cases with Alzheimer's disease (AD) and dementia with Lewy bodies at postmortem. In one study looking particularly at focal presentations of AD, 7% of cases with a bvFTD syndrome had AD pathology (Alladi et al. 2007).

BvFTD is a clinically, neuroanatomically, genetically and pathologically heterogeneous disorder without a clear correlation between the clinical and neuroanatomical phenotype observable in life and the underlying pathogenetics. Over the next few years, there is an increasing likelihood that there will be trials of targeted disease-modifying agents aimed at the underlying pathology in bvFTD (Knopman et al. 2008). However, unless there is a reliable and objective way in which this can be identified, initiating such trials will be difficult. With this in mind, this review will assess the extent to which it is currently possible to define bvFTD pathological subtypes in vivo and investigate potential biomarkers that may improve diagnostic specificity.

Current and Future Biomarkers for bvFTD

It would be helpful to be able to make a diagnosis of bvFTD-tau, bvFTD-TDP or bvFTD-FUS during life (Table 3), with the ultimate aim of separating each of these pathologies into their subtypes. What biomarkers are currently available to make these diagnoses and what may be useful in the future?

Clinical and Neuropsychological Data

Are there any clinical features which could be important markers of underlying pathology? Most previous investigations have been disappointing, with different studies revealing conflicting results between different pathologies in age at onset or behavioural symptoms (Hodges et al. 2004; Knopman et al. 2005; Kertesz et al. 2005; Bian and Grossman 2007). Other studies have shown behavioural and neuropsychological differences at a group level, e.g. in one study, patients with tau-positive pathology were more likely to have poor planning and judgment compared to tau-negative patients who had impaired personal conduct but few dysexecutive symptoms (Hu et al. 2007a); another study suggested tau-positive patients were more likely to have visual perceptual–spatial difficulties and an extrapyramidal disorder compared to tau-negative patients who were more likely to have difficulties with social and verbally mediated executive functions (Grossman et al. 2007); lastly, in FTLD-tau patients, those with four-repeat tauopathies (CBD or PSP) were more likely to display behavioural underactivity than those with three-repeat tauopathies (PiD) (Hu et al. 2007b). However, it is unclear

Table 3 Biomarkers and diagnostic features of bvFTD-tau, bvFTD-TDP and bvFTD-FUS

Diagnosis	Current biomarker	Future biomarker	Highly suggestive of diagnosis
bvFTD-tau	*MAPT* mutation analysis	Tau forms in CSF ?Tau ligand PET scan	PSP clinical syndrome
bvFTD-TDP	*GRN* mutation analysis Plasma *GRN*	TDP-43 in CSF or plasma ?TDP-43 ligand PET scan	MND/ALS clinical syndrome
bvFTD-FUS	None	?FUS ligand PET scan	Very young onset

whether these group differences can translate into useful diagnostic features at a single patient level.

More promisingly, recent descriptions of patients with FUS pathology have suggested that there may be a number of clinical features which could help to discriminate them from other FTLD patients (Neumann et al. 2009; Seelaar et al. 2010, 2011; Josephs et al. 2010; Rohrer et al. 2011; Urwin et al. 2010; Loy et al. 2010; Snowden et al. 2011). These studies have looked particularly at the aFTLD-U subtype of FTLD-FUS which usually presents with bvFTD, unlike the NIFID or BIBD subtypes which have a more heterogeneous clinical presentation. aFTLD-U cases are mostly sporadic, with a very early onset of disease in some cases—in one large series, the mean age of onset was 41 (Urwin et al. 2010), with the youngest case reported of aFTLD-U having an onset of 22 (Snowden et al. 2011). One study suggested that sporadic bvFTD with an onset under 40 would be highly predictive of aFTLD-U (Loy et al. 2010)—in this small series of 64 cases, one case was identified which fitted this criteria and was in fact a case of aFTLD-U. Larger studies will be needed to investigate how specific this finding is, but it is unlikely to be very sensitive as a number of aFTLD-U cases over the age of 40 have been reported (Seelaar et al. 2010, 2011; Rohrer et al. 2011; Snowden et al. 2011). Clinically, initial reports suggested that the presence of hallucinations or delusions was more prevalent in aFTLD-U than other pathologies. However, in the largest series, only 36% of cases had one or both of these features (Urwin et al. 2010), and hallucinations and delusions have been reported in other FTLD pathologies, particularly FTLD-TDP in association with clinical MND/ALS (Omar et al. 2009; Lillo et al. 2010). In a recent report, it was suggested that aFTLD-U cases have a stereotyped behaviour-predominant clinical subtype of bvFTD characterized by obsessionality, repetitive behaviours and rituals (Snowden et al. 2011). Other behaviours such as hypersexuality have also been suggested as possible defining features of aFTLD-U (Urwin et al. 2010; Snowden et al. 2011). However, it remains unclear what the specificity and sensitivity are for these clinical features.

The presence of certain neurological features may also be helpful, e.g. an associated PSP syndrome is highly predictive of underlying FTLD-tau pathology (usually PSP), whilst an associated MND/ALS syndrome is highly predictive of FTLD-TDP (either type 2 or type 3 in the Sampathu classification). These can be helpful if they occur early on in the disease when patients are likely to enter into clinical trials, but will be less useful if they occur (as they sometimes do) later on in the disease. CBS is less predictive of a particular pathology (Ling et al. 2010) and can be associated with FTLD-tau, FTLD-TDP or rarely FTLD-FUS.

Neuroimaging

By definition, the presence of frontal and/or temporal lobe atrophy is usually seen in bvFTD, although the presence of parietal lobe atrophy has also been described (Rohrer et al. 2008; Whitwell et al. 2009a). In a cluster analysis, one study suggested that there were four neuroanatomical subtypes of bvFTD: frontal-dominant, temporal-dominant, frontotemporal and temporofrontoparietal (Whitwell et al. 2009b). How do these map on to pathological subtypes? In a subgroup of patients in the study with genetic and pathological confirmation, the temporal-dominant group consisted entirely of patients with *MAPT* mutations, and this is consistent with other studies of genetic subgroups in bvFTD which suggest that *MAPT* mutations are associated with relatively symmetrical temporal lobe atrophy (Whitwell et al. 2009a; Rohrer et al. 2010b). However, the other neuroanatomical subtypes were more heterogeneous with no clear correlations, e.g. some studies have suggested that parietal lobe involvement may be a feature of patients with *GRN* mutations/FTLD-TDP type 3 (Sampathu classification), but in this study, only 30% of the temporofrontoparietal cases had this pathology (Whitwell et al. 2009a). At a group level, conflicting results have been shown in studies comparing FTLD-tau with FTLD-U cases, with some showing differences (e.g. Kim et al. 2007) and others showing very similar patterns of atrophy (e.g. Pereira et al. 2009). As with clinical and neuropsychological data, it does not seem that at a single case level structural neuroimaging will be an adequate diagnostic biomarker.

Unlike structural imaging, PET imaging has the ability to label specific proteins and thus the potential to allow for specific in vivo diagnosis. Amyloid-labelling tracers such as ^{11}C Pittsburgh Compound B are now used in research studies as a marker of AD pathology. It may therefore be possible to exclude cases in FTLD clinical trials with AD pathology by using PET imaging. The development of ^{18}F amyloid-labelling compounds is likely to increase the use of such technology further. The development of PET ligands that could bind to tau, TDP-43 or FUS would be a major advance in the molecular diagnosis of bvFTD.

Blood

Finding a pathogenic mutation in *GRN*, *MAPT* or one of the rare mutations allows a pathological diagnosis to be made in life. This makes these particular patient groups ideal for initial trials of disease-modifying therapy. In patients with *GRN* mutations, plasma progranulin level can predict the presence of a mutation and may be an easier and more cost-effective screening method (Coppola et al. 2008; Ghidoni et

al. 2008; Finch et al. 2009). Preliminary studies looking at plasma TDP-43 levels have unfortunately not shown that they are able to differentiate between different subgroups (Foulds et al. 2008; Foulds et al. 2009), but further work continues in this area.

Cerebrospinal Fluid

Early CSF studies tended to contrast clinically diagnosed cohorts of bvFTD with patients with Alzheimer's disease with conflicting results in the most commonly used biomarkers of total tau, phosphorylated tau and Aβ42 (Riemenschneider et al. 2002; Pijnenburg et al. 2004; Grossman et al. 2005). However, one more recent study of pathologically confirmed cases has suggested that the total tau to Aβ42 ratio is sensitive and specific at discriminating between FTLD and AD, being significantly higher in AD (Bian et al. 2008). Some studies are now looking at particular tau forms and whether these are more specific: early work suggests they could be important in identifying PSP syndromes (Borroni et al. 2008, 2009). As with serum levels, measurement of TDP-43 is promising (Steinacker et al. 2008; Kasai et al. 2009), and further studies in pathologically confirmed cases will be important. Few studies have looked at more novel biomarkers, but one recent report looking at multiple possible CSF biomarkers was able to identify ten analytes that differed between FTLD-TDP and FTLD-tau, with the top five (IL-17, Eotaxin-3, ACTH, Fas and Aguti-related protein) used in an analysis that classified the two groups with 86% sensitivity and 78% specificity (Hu et al. 2010). Further such studies will be important in developing new CSF biomarkers in order to separate bvFTD patients into their respective pathologies.

Summary

Behavioural variant frontotemporal dementia is heterogeneous, and although revised diagnostic criteria will be important in making a more uniform clinical diagnosis across centres, they will not help in separating patients into pathological subtypes: bvFTD-tau, bvFTD-TDP and bvFTD-FUS. Accurate diagnosis in life is currently possible only by the identification of a pathogenic mutation in one of the FTLD genes. Whilst there are some suggestive features for certain pathological subtypes, e.g. very young onset in bvFTD-FUS, the presence of a PSP syndrome in bvFTD-tau and the presence of an MND/ALS syndrome in bvFTD-TDP, these are limited. Being able to image tau, TDP-43 or FUS pathology using PET or to use serum or CSF markers to distinguish these pathologies would be a major step forward in the field.

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Conflicts of interest None.

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