

Fluid biomarkers in frontotemporal dementia: past, present and future

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Abstract

The frontotemporal dementia spectrum (FTD) of neurodegenerative disorders includes a heterogeneous group of conditions. However, following on from a series of important molecular studies in the early 2000's, major advances have now been made in the understanding of the pathological and genetic underpinnings of the disease. In turn, alongside the development of novel methodologies for measuring proteins and other molecules in biological fluids, the last ten years has seen a huge increase in biomarker studies within FTD. This recent past has focused on attempting to develop markers that will help differentiate FTD from other dementias (particularly Alzheimer's disease, AD) as well as from non-neurodegenerative conditions such as primary psychiatric disorders. Whilst, CSF, and more recently blood, markers of AD have been successfully developed, specific markers identifying primary tauopathies or TDP-43 proteinopathies are still lacking. More focus at the moment has been on more non-specific markers of neurodegeneration, and in particular, multiple studies of neurofilament light chain have highlighted its importance as a diagnostic, prognostic and staging marker of FTD. As clinical trials get underway in specific genetic forms of FTD, measures of progranulin and dipeptide repeat proteins in biofluids have become important potential measures of therapeutic response. However, understanding of whether drugs restore cellular function will also be important, and studies of key pathophysiological processes including neuroinflammation, synaptic health and lysosomal function are also now becoming more common. There is much still to learn in the fluid biomarker field in FTD, but the creation of large multinational cohorts is facilitating better powered studies, and will pave the way for larger -omics studies, including proteomics, metabolomics and lipidomics, as well as investigations of multimodal biomarker combinations across fluids, brain imaging and other domains. Here we provide an overview of the past, present and future of fluid biomarkers within the FTD field.

Introduction

The frontotemporal dementia spectrum (FTD) encompasses a group of conditions that overlap in their clinical, neuroanatomical, genetic and pathological features^{1,2}. Clinically, FTD can be divided into a behavioural variant (bvFTD), a language variant (primary progressive aphasia (PPA)) and a motor presentation (either amyotrophic lateral sclerosis (FTD-ALS) or an atypical parkinsonian disorder). Neuroanatomically, the FTD spectrum is characteristically associated with dysfunction and neuronal loss in the frontal and temporal lobes, but more widespread cortical, subcortical, cerebellar and brainstem involvement is now recognized³. Genetically, around a third of FTD is familial with autosomal dominant mutations in three genes accounting for most of the inheritance: *GRN* (progranulin), *C9orf72* (chromosome 9 open reading frame 72) and *MAPT* (microtubule-associated protein tau)^{2,4,5}. Lastly, pathologically, cellular inclusions containing abnormal forms of tau, TDP-43 or FET proteins are found in the majority of people with an FTD syndrome⁶. The interaction between clinical phenotype, neuroanatomy, genotype and pathology is complex (Figure 1) and means that FTD can be hard to diagnose (particularly its specific pathological form during life) and difficult to track over time.

One way that researchers have aimed to solve some of these outstanding issues in the FTD field has been to develop fluid biomarkers, and there has been a growing literature in recent years investigating new cerebrospinal fluid (CSF) or blood measures in people with FTD. This review aims to set out what has been done so far, where we are at present, and what we still need to achieve in the future within the FTD fluid biomarker research world. This is particularly

important in a time when potential therapies have now been developed and clinical trials have started.

Classification and use of biomarkers in FTD

Fluid biomarkers, measured typically in CSF, serum or plasma [Box 1] using a variety of different techniques [Box 2], are objective indicators of normal or pathological biological processes, or pharmacological responses to a therapeutic intervention⁷. In FTD, biomarkers can be classified in a number of ways⁸:

- *Diagnostic*, including distinguishing FTD vs non-neurodegenerative disorders and FTD vs Alzheimer's disease (AD) or other dementias, as well as identifying the particular pathological form of FTD.
- *Prognostic*, allowing prediction of likely disease course and survival.
- *Staging*, including particularly for the genetic forms of FTD, whether someone is presymptomatic, nearing symptom onset (proximity markers), or phenoconverting.
- *Therapeutic response*, including showing target engagement and efficacy, as well as pharmacokinetic and pharmacodynamic responses.

Biomarkers can also provide an insight into the underlying pathophysiology of FTD, and in the context of clinical trials, could offer a direct experimental medicine approach to understanding molecular mechanisms through measurement of biofluids pre- and post-intervention. Whilst some pathways are specific to one or other pathogenetic form of FTD, studies in recent years have

particularly highlighted the importance of loss of synaptic integrity⁹⁻¹³, lysosomal dysfunction^{14,15} and neuroinflammation¹⁶⁻¹⁸ as major pathophysiological mechanisms across the FTD spectrum.

Differentiating FTD from other dementias and from non-degenerative disorders

In the neurodegenerative biomarker field, much effort has been made in being able to differentiate AD from other dementias. Many of these studies have included an FTD cohort as a comparator group. Until recently, the focus has been on (usually combined) measures of tau (both 'total' and phosphorylated forms) and amyloid-beta ($A\beta$) in CSF. For example, a raised tau/ $A\beta$ 42 ratio identifies those with likely pathological AD (e.g. Paterson et al., 2018¹⁹) in comparison with those with likely FTD where the ratio is lower. Clinically, this is helpful in identifying atypical presentations of AD, both in bvFTD (where such markers are an exclusionary diagnostic criterion²⁰) and PPA, where the logopenic variant is usually an AD rather than FTD disorder pathologically²¹. More recent studies have investigated blood-based markers of AD, showing that plasma phosphorylated tau-181 and tau-217 are raised in AD but not FTD (apart from those with specific *MAPT* mutations that lead to accumulation of paired helical filament tau pathology similar to AD, e.g. R406W and V337M)²²⁻²⁵. This overall result was recently confirmed for plasma p-tau181 in a study with neuropathological confirmation (ref: PMID: 32720099).

As an aside, one interesting point of note that has arisen from these studies has been the finding that $A\beta$ species including $A\beta$ 38, $A\beta$ 40 and sAPP β are commonly lowered in FTD compared with controls²⁶⁻³², with the reason for this remaining unclear at present.

As well as difficulties in differentiating FTD from AD clinically on occasion, there can also be problems with differentiating FTD from non-neurodegenerative disorders at times, including those with primary psychiatric disorders. Recent studies have shown that changes in non-specific markers of degeneration (such as neurofilament light chain protein (NfL) [Box 3]) may be helpful in this setting^{33,34}.

Diagnosing pathogenetic forms of FTD during life

Genetic FTD

FTD is genetic in around one third of people, with expansions in *C9orf72* the most common cause and usually tested for through PCR and confirmed with Southern blotting. Mutations in the other common causes, *GRN* and *MAPT*, as well as the rarer genetic groups *TBK1*, *TARDBP*, *VCP*, *FUS*, *CHMP2B*, *SQSTM1*, and *UBQLN2* are commonly tested for through either a next generation sequencing panel, or increasingly commonly through exome or genome sequencing⁵. However, for two of the major genetic causes of FTD (*GRN* mutations and *C9orf72* expansions), there are specific biomarkers that can identify people who carry pathogenic mutations:

Progranulin

The majority of pathogenic variants in *GRN* are frameshift, nonsense or splice site mutations and cause haploinsufficiency, resulting in reduced levels of progranulin protein (Figure 2A). This is measurable in both blood and CSF³⁵⁻³⁷, although the majority of studies have been performed in blood. Whilst initial studies showed a very high sensitivity and specificity (both >95%) with a cut off of 61.5ng/ml (measured in plasma by the Adipogen assay^{24,25}), a more recent study suggests a

higher cut off of 71.0ng/ml⁴⁰ (sensitivity 98.1%, specificity 98.5%). Levels seem to be low from the earliest they have been measured (late teens) with the assumption that they are decreased from birth, and with levels relatively constant over time (at least over 4 years in one study⁴⁰). In general, this makes measuring progranulin levels in blood a highly accurate (and less expensive) way of detecting a pathogenic mutation prior to (more expensive) genetic screening, as well as a way of confirming likely pathogenicity in splice site or missense variants (the latter more commonly being risk factors rather than directly pathogenic⁴¹). Levels in controls are very variable (e.g. from below the cut-off point to >250ng/ml in plasma) with the presence of a metabolic syndrome, autoimmune disease, obesity, and cancer affecting levels as well as certain genetic factors (*GRN* rs5848 polymorphism⁴² and *SORT1* rs646776 polymorphism^{43,44}). CSF progranulin has been studied less than blood with no clear cut-off defined for the presence of a *GRN* mutation at present, and a relatively weak correlation seen between CSF and blood (e.g. $r=0.54$ in *GRN* mutation carriers, and $r=0.21$ in healthy controls in one study: Meeter et al, 2016³⁶). In fact, although the concentration of progranulin in blood is about 20 times higher than in CSF, most progranulin in CSF is brain-derived (with a calculated intrathecal fraction of 86%⁴⁵). Lastly, the majority of studies have used a small set of (non-fully validated) commercially available ELISAs to measure progranulin concentrations so far (e.g. Adipogen, R+D, Biovondor), and whilst concentrations seem highly correlated between assays⁴⁶, absolute levels are different. Although the epitopes detected by the capture and detection antibodies are not known (or available) for these assays, the high correlation suggests that they may well measure similar forms of progranulin but that they have not been standardised to each other: a certified reference material and an external quality control programme for progranulin would solve this issue and would

allow for standardisation of reference and decision limits across assays and laboratories. Nonetheless, these assays are already being used (with laboratory-specific reference and decision limits) not just clinically to detect the presence of mutations, but also to detect treatment response in therapeutic trials e.g. in an early phase trial of a monoclonal antibody against sortilin, plasma and CSF progranulin levels were reported to have been increased back into the normal range following treatment⁴⁷.

Dipeptide repeat proteins

C9orf72-related FTD/ALS is caused by a hexanucleotide repeat expansion in the non-coding region of the gene⁴⁸. The pathogenic repeat size varies from probably more than around 30 to thousands, although the lower limit of pathogenicity remains undetermined. One of the key mechanisms of toxicity of large expansions is the production of dipeptide repeat proteins (DPRs) by repeat-associated non-AUG (RAN) translation: C9orf72 RNA repeats can be translated through RAN translation producing five DPRs poly(GA), poly(GR), poly(PR), poly(PA) and poly(GP). A number of studies have tried to measure levels of these DPRs in CSF, and so far only poly(GP) levels have been found to be measurable, with raised levels in both the presymptomatic and symptomatic period (Figure 2B) independent of clinical phenotype or stage of disease⁴⁹⁻⁵¹. Although not currently used clinically, it may become more widely used in a similar way to progranulin levels, allowing detection of an expansion prior to genetic screening (particularly if DPRs could be detected peripherally rather than in CSF). However, its more common use is likely to be as an important biomarker of treatment response in therapeutic trials e.g. in forthcoming antisense oligonucleotide therapy trials. So far, biomarker studies have used the MSD platform

(see Box 2), with the current assay showing levels overlapping with controls in some *C9orf72* expansion carriers – future studies using more sensitive techniques such as Simoa [Box 2] may improve the dynamic range of the assay and separation of cases from controls, which will be very important for therapeutic trials aiming to show a decrease in level with treatment.

Other genetic causes of FTD

There are currently no specific biomarkers that can identify *MAPT* mutations in biofluids nor any of the rarer genetic causes. *TBK1* mutations, similarly to *GRN*, are usually frameshift, nonsense or splice site, and cause haploinsufficiency – it would therefore be theoretically possible to predict the presence of a pathogenic mutation through the detection of reduced *TBK1* protein levels in blood or CSF, although no reliable methods are currently available.

Sporadic FTD

Determining the pathological nature of sporadic forms of FTD during life is much more difficult than the genetic forms. Around 50% of sporadic FTD is associated with a TDP-43 proteinopathy, 45% with a tauopathy, and 5% with a FUS/FET proteinopathy, but specific biomarkers for the presence of these proteins do not currently exist:

TDP-43

TDP-43 proteinopathies are characterized by insoluble neuronal cytoplasmic or intranuclear inclusions and glial cytoplasmic inclusions, which aggregate in the cells^{52,53}. Cell death results in the release of TDP-43 and, therefore, its levels in CSF may increase. ‘Total’ TDP-43 levels have

been measured in CSF with levels found to be higher than controls in some studies^{54,55,56} but with substantial overlap with controls and those with tauopathies⁵⁷, and therefore poor diagnostic accuracy for the presence of a TDP-43 proteinopathy. Similar findings of raised TDP-43 have been found in blood⁵⁸ with overall concentrations much higher than those seen in CSF. In fact, the total TDP-43 blood to CSF ratio is about 200:1, with one study suggesting that when found in CSF this form of TDP-43 actually originates from the blood⁵⁹.

Discovering a pathogenic (or pathology-associated) form of TDP-43 to measure in biofluids has led to studies of phosphorylated forms of TDP-43 (pTDP-43) and whilst this has been detected in plasma of patients at higher concentrations than controls^{60,61}, again there was substantial overlap with controls. No studies have managed to measure pTDP-43 in lumbar CSF so far⁶².

Tau

Primary tauopathies include Pick's disease, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), globular glial tauopathy and *MAPT* mutations. So far, no specific tau biofluid measures of these disorders have been discovered. CSF concentrations of 'total' tau and phosphorylated forms of tau (p-tau181 and p-tau231) are variable in the different forms of FTD, but overall, are generally lower than in AD. Studies of tau protein fragments have so far not yielded any specific primary tauopathy markers^{63,64}. More promising assays may arise from the real-time quaking-induced conversion (RT-QuIC) method which is currently under investigation for Pick's disease and the 4R-tauopathies⁶⁵⁻⁶⁷.

FUS/FET

These proteinopathies are rare causes of FTD, and as yet no studies have shown their presence in CSF or blood.

Specific molecular pathways in FTD

Whilst, some molecular processes occur across different forms of FTD, each pathogenetic form has unique features. Here we focus on studies of specific disease-associated proteins and unbiased proteomic investigations performed in specific forms of FTD.

Progranulin

Progranulin is a glycoprotein found mainly in neurons and microglia, and is involved in numerous cellular processes (Figure 3) including neuroinflammation, lysosomal function and growth⁶⁸. It is a precursor protein, broken down into a number of smaller proteins, known as granulins 1-7 (previously known as A-G) and para-GRN⁶⁹. These proteins have key lysosomal and inflammatory roles and have been shown to promote TDP-43 accumulation and toxicity^{70,71}. However, due to their size and a lack of specific antibodies, granulins have yet to be measured in biofluids. Nonetheless, they may prove to be important measures of treatment response in trials of *GRN*-targeted therapies e.g. unpublished work from one company show that their compound increases lysosomal granulins whilst a sortilin-blocking monoclonal antibody decreases them in iPSC-derived neurons⁷². A mass spectrometric approach to the identification of specific progranulin breakdown fragments may be required.

Other proteins closely associated with progranulin include prosaposin, sortilin and secretory leukocyte protease inhibitor (SLPI). Prosaposin, similarly to progranulin, performs different functions both intra- and extracellularly, including regulation of lysosomal enzymes and neuroprotection of glial cells⁷³. It is also a precursor protein, broken down into 4 saposins, which are involved in the breakdown of sphingolipids⁷³. Progranulin binds to prosaposin and both proteins are trafficked into the lysosome⁷⁴, with studies showing that progranulin is important in mediating prosaposin and saposin levels in both neuronal and glial cells⁷⁵. No studies of prosaposin concentrations have yet been reported in FTD. Sortilin, a member of the Vps10p domain receptor family, is involved in the endocytosis of progranulin into the lysosome, forming a key receptor in progranulin functioning⁷⁶. Sortilin levels have been measured in the biofluids of aging individuals, showing a strong positive correlation with progranulin levels in CSF but not in plasma⁴⁴ but have yet to be measured in those with *GRN* mutations. SLPI is an inhibitor of the serine protease, elastase, which is known to break down progranulin into the granulins. Levels have been investigated in one study⁷⁷ which showed significantly higher plasma concentrations in symptomatic *GRN* mutation carriers compared to both presymptomatic mutation carriers and controls. Interestingly, higher SLPI levels were associated with a later age of onset with the authors suggesting that SLPI had a role in regulating penetrance⁷⁷.

An unbiased proteomic study using mass spectrometry in CSF samples of *GRN* mutation carriers, showed significantly reduced levels of five proteins in symptomatic patients compared with controls: neuronal pentraxin receptor (NPTXR), receptor-type tyrosine-protein phosphatase N2, neurosecretory protein VGF, chromogranin-A, and V-set and transmembrane domain-containing

protein 2B⁷⁸. More work is needed to understand how specific these markers are to *GRN* mutation carriers (as many were also found to be abnormal in *C9orf72* and *MAPT* mutation carriers as well)⁷⁸ and what their role is in the *GRN* pathophysiological pathway.

C9orf72

Less is known about other interacting proteins within the *C9orf72* pathways and few proteomic studies have been performed. However, a recent study compared the CSF proteome of *C9orf72*-associated FTD and *C9orf72*-associated ALS and showed over 200 proteins were significantly different between the groups with neurofilament medium polypeptide, chitotriosidase, and ubiquitin carboxyl-terminal hydrolase isozyme L1 amongst the proteins higher in the ALS group, and NPTXR decreased in the FTD group⁷⁹. As trials of *C9orf72* mutation carriers may well include both people with ALS and FTD, it will be important to better understand which biomarkers are specific to *C9orf72*-related disease across the phenotypes, which are specific to one or other of *C9orf72*-associated FTD or *C9orf72*-associated ALS, and which are abnormal due to the presence of FTD or ALS independent of the fact the syndrome is due to a *C9orf72* expansion⁷⁹. Such studies may also help in prediction of the subsequent phenotype in asymptomatic mutation carriers.

Neuroinflammation, lysosomal function and synaptic health – major molecular mechanisms of FTD

Markers of neuroinflammation (Table 1)

Neuroinflammation is a complex and multistage process involving activation of specific cells within the central nervous system (mainly microglia and astrocytes) and release of a series of pro- and anti-inflammatory factors. Recent evidence suggests that dysregulation of neuroinflammatory mechanisms may be involved in the pathophysiological process of FTD (reviewed in Bright et al., 2019¹⁸). As expected from such a complex process, there are multiple molecules that can be measured, each highlighting dysfunction of specific parts of the inflammatory response. Here, we divide them into firstly, markers of glial cell activation, secondly, cytokines and chemokines, thirdly, the complement system, and finally, the resolution pathway. Related to neuroinflammation, disruption of the blood-brain barrier and angiogenesis may well also play a part in the pathophysiology of FTD, and are reviewed in this section as well.

Glial cell activation

Glial cells, such as microglia and astrocytes, are pivotal to the inflammatory response in the brain. This glial activation leads to the production of inflammatory cytokines and chemokines, which induce changes in cell differentiation and morphology in response to stress¹⁸. Different fluid biomarkers of glial activation have been measured, including sTREM2 (soluble triggering receptor expressed on myeloid cells 2) and macrophage-derived chitinases including chitotriosidase (CHIT1) and YKL-40 (otherwise known as chitinase-3-like protein 1 or CHI3L1).

Whilst TREM2 appears to be a marker of microglial activation in AD⁸⁰, its status in FTD remains uncertain. Some studies have shown increases in an FTD cohort⁸¹ whilst others have only shown increases when the cohort is stratified into specific pathogenetic forms⁸².

Similarly to TREM2, the chitinase proteins have been shown to be increased in the CSF of some cohorts but not others^{29,30,79,83,84,85}, with some forms of FTD more likely to show increases than others (e.g. those with associated ALS). Larger sample sizes in more well-defined cohorts are needed here including examination within presymptomatic mutation carriers in genetic forms of FTD. Plasma levels of the chitinases have generally been found to be similar to controls^{86,87} in all groups investigated so far.

Glial fibrillary acidic protein (GFAP), a marker of astrocytic activation/astrogliosis, has also been measured at increased levels in the CSF of people with FTD^{86,88}. Whilst levels in plasma were not elevated in an initial study⁸⁶, a more recent report in a large genetic cohort showed that GFAP was significantly increased in symptomatic *GRN* mutation carriers⁸⁹ with levels likely to be increasing just prior to symptom onset.

Cytokines and chemokines

Cytokines and chemokines are factors produced by glial cells in response to stressors and quite a number have now been measured in different FTD biomarker studies (Table 1).

CSF levels of a proinflammatory CC family cytokine, RANTES, are significantly reduced in both an unspecified FTD cohort and *GRN* mutation carriers compared to controls⁹⁰. Conversely, MCP-1, another proinflammatory cytokine of this family, is increased in the CSF of an FTD cohort overall and unchanged in *GRN* mutation carriers, suggesting complex underlying mechanisms.

However, in both cases, this was not mirrored in serum, highlighting differences between the biological fluids and the need for further investigation. Similar paradoxical findings have been shown in other studies e.g. levels of the proinflammatory interleukin, IL-6, have been shown to be increased in FTD (in plasma) and in PSP (in serum and CSF) and yet CSF levels for the anti-inflammatory interleukin, IL-8, appear to also be increased in FTD compared to controls⁹¹⁻⁹⁴. This may simply demonstrate the complexity of the inflammatory signature of FTD but could also indicate the importance of stratifying cohorts by pathology, clinical diagnosis, genetic group or disease stage. For example, one study which stratified their cohort by pathology, showed that CSF levels of proinflammatory interleukins, IL-17 and IL-23 were significantly reduced in those with TDP-43 pathology compared to those with tau pathology, whereas the TNF family of cytokines, TRAILR3 and FasL were significantly increased in those with TDP-43 pathology compared with those with tau pathology⁹⁵. Following this trend, a number of cytokines and chemokines are significantly different in *GRN* mutation carriers compared to non *GRN*-FTD, including the interleukins IL-15, IL-17, the CXC family cytokine IP-10 and TNF family cytokine, $TNF\alpha$ ⁹⁰.

The complement system

There is some evidence to suggest a role for the complement system in the pathology of FTD but only a small number of studies have so far examined complement proteins in biofluids. One study showed no difference in *GRN* mutation carriers compared to controls in either CSF C1qa and C3b although both measures increased as cognition declined in the cohort¹¹, whilst another study showed raised C4d in patients with PSP⁹⁶.

Resolution pathway

Resolution of inflammation is the process that takes place to return the tissue to a homeostatic condition. During resolution, there are specialized pro-resolving mediators (SPMs) that are synthesized in endothelial cells, macrophages and neutrophils and actively participate in the transition from a proinflammatory state to a homeostatic one⁹⁷. Only one study so far has explored alterations in SPMs in CSF and plasma so far, showing decreased levels of annexin1 in the plasma of people with bvFTD compared with AD and controls⁹⁸.

Blood-brain barrier

The blood-brain barrier (BBB) is also an important aspect of the body's response to stressors and a number of neuropathological studies suggest that it can be affected in neurodegeneration. However, as the BBB is a physical barrier a real neurochemical marker for this does not exist. Often the albumin CSF/blood ratio is claimed to be a marker for the BBB, but the albumin quotient more likely represents the CSF flow and is therefore perhaps better thought of as a measure of the CSF-blood barrier^{99,100}. If this flow is affected, higher levels of albumin will be present in the CSF, giving an increased albumin CSF/serum ratio¹⁰¹. In FTD, the levels in an unspecified cohort are variable without any significant difference from controls^{102,103} but studies of better phenotyped groups are needed.

Angiogenesis

Although not part of the inflammation pathway specifically, angiogenesis i.e. the formation of new blood vessels, can occur with impaired BBB function and is stimulated by activated immune cells. Vascular endothelial growth factor (VEGF) levels are increased in the CSF of people with FTD¹⁰⁴, as are levels of another member of the VEGF family, placental growth factor¹⁰⁵, as well as angiogenin¹⁰⁶. Platelet-derived growth factor subunit B has been shown to be increased in the serum of a PSP/CBS group compared with controls¹⁰⁷, but other angiogenic factors have not been well studied. However, initial investigations of matrix metalloproteinases (MMPs), involved in angiogenesis as well as other processes (MMP-2 and MMP-9), show alterations in an FTD cohort¹⁰⁸.

Markers of lysosomal function (Table 2)

The function of the lysosome in a cell is to breakdown and recycle proteins, ensuring cellular homeostasis and survival. Abnormal lysosomal function has been described in FTD in cellular models but few markers of this have been measured so far in biofluids. One study has shown that lysosomal-associated membrane protein 1 (LAMP1) levels are significantly higher in plasma exosomes from people with AD patients but not FTD¹⁰⁹. However, limited sample sizes restricted the further stratification of the FTD group which is likely to be an important factor, e.g. in a study of CSF from people with pathologically-confirmed PSP and CBD, LAMP1 and LAMP2 were increased in CBD, whilst another marker lysozyme was increased in both PSP and CBD compared with controls¹¹⁰.

A group of cysteine proteases, known as cathepsins, may also form promising markers of lysosomal function in FTD e.g. cathepsin D levels measured in plasma exosomes are significantly higher in FTD and AD compared to controls¹⁰⁹. However, research into these enzymes is relatively limited so far.

Lastly, and as also discussed above, a number of the proteins involved in the pathophysiology of *GRN*-related FTD are key to lysosomal function, including prosaposin (and the saposins), as well as glucocerebrosidase¹¹¹. Other lysosomal enzymes have been poorly studied in FTD, although one study showed lower levels of alpha-mannosidase in CSF compared with healthy controls¹¹².

Markers of synaptic and neurotransmitter function (Table 3)

Progressive synaptic dysfunction and loss has been shown to occur in FTD, and therefore it is reasonable to expect that any changes in synaptic proteins in brain tissue may be reflected in changes within the CSF (or potentially the blood) of people with FTD.

Presynaptic markers

One study recently compared the levels of the synaptic proteins SNAP-25 and synaptotagmin in CSF samples from people with AD and FTD and age-matched controls. SNAP-25 binds to synaptobrevin in the presynaptic plasma to form the soluble NSF attachment protein receptor (SNARE) complex¹¹³, involved in vesicle fusion and release of neurotransmitters, whilst synaptotagmin is a vesicle protein that acts as a Ca²⁺ sensor triggering vesicle fusion upon calcium influx¹¹⁴. None of the synaptic proteins showed altered levels in FTD patients when

compared to controls but both of them were increased in an AD cohort¹¹⁵. This is in contrast to a previous study that measured exosome-derived proteins in plasma within a group of people with FTD and showed decreased levels of synaptotagmin, as well as synaptophysin, the most abundant integral synaptic vesicle protein that regulates SNARE assembly and vesicle fusion¹¹⁶. In this same study, GAP-43, another presynaptic protein that interacts with the SNARE complex and plays a role in Ca²⁺-dependent vesicle fusion¹¹⁷ was not altered in FTD, whereas the peripheral vesicle protein synapsin 1, involved in vesicle trafficking, was increased¹¹⁶.

Whilst beta-synuclein, a further candidate presynaptic marker, has only shown elevation in the CSF of those with AD and not FTD¹¹⁸, other potential markers for FTD include Rab3A, a protein essential in intracellular transport and in sustaining a reserve of vesicles ready for release¹¹⁴ which is decreased in the tissue of people with FTD and shows promise as a CSF marker of synapse loss in other disorders¹¹⁹, and synaptic vesicle glycoprotein 2A (SV2A), currently under investigation to measure synaptic density with PET imaging but not yet measured in CSF.

Postsynaptic markers

Neurogranin is involved in long-term potentiation and synaptic plasticity and regulates intracellular Ca²⁺ concentration. Increased concentrations of neurogranin in CSF in AD predict cognitive decline from MCI to AD¹²⁰. In FTD, levels of neurogranin in CSF seem to remain unchanged when compared to controls¹¹⁵. However, when measured in exosomes in plasma, neurogranin was significantly decreased when compared to controls in FTD¹¹⁶. Synaptopodin

regulates intracellular Ca²⁺ concentration and decreased levels were also shown in the same study¹¹⁶.

Other synaptic markers

Reelin is an extracellular matrix glycoprotein with roles including regulation of filopodia formation, dendrite growth and spine formation, and synaptogenesis, as well as modulation of synaptic plasticity and neurotransmitter release¹²¹. One small study has previously shown increased levels in FTD in CSF compared with controls¹²².

Recent studies have investigated the neuronal pentraxin (NPTX) family of proteins as synaptic dysfunction markers^{79,123}. NPs are multifunctional proteins implicated in synaptic plasticity. Decreased CSF levels of neuronal pentraxin receptor (NPTXR) have been shown in symptomatic genetic FTD¹²³ whilst neuronal pentraxin 2 (NPTX2) is decreased in symptomatic *GRN* and *C9orf72* mutation carriers but not in *MAPT* mutation carriers. Levels of NPTX2 in CSF correlate with disease progression and NfL levels, and can predict symptom onset¹²³.

Neurotransmitter release

Serotonergic, dopaminergic, glutamatergic, and GABAergic pathways have all been shown to be altered in FTD¹²⁴. One study has reported that increased activity of dopaminergic neurotransmission and altered serotonergic modulation of dopaminergic neurotransmission is associated with agitated and aggressive behaviour whereas degeneration of the noradrenergic neurotransmitter system might contribute to the cognitive deficits in FTD¹²⁵.

An increase in dopamine (DA) and a decrease in its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) have been reported in CSF and blood in people with FTD and ALS when compared to controls and the ratio of DOPAC to DA is able to discriminate FTD from ALS¹²⁶.

Circulating nucleic acids

Whilst most DNA and RNA is found within cells, some nucleic acids are found circulating within the blood as well as other body fluids including CSF. Whilst cell-free DNA (cfDNA) studies are underway in FTD¹²⁷, little has been reported about their role so far. However, more studies have focused on microRNAs (miRNAs), small noncoding RNA molecules involved in regulation of gene expression¹²⁸. At present, most studies have investigated whether single miRNAs or combinations of multiple miRNAs in blood or CSF are able to differentiate FTD syndromes from controls or other neurodegenerative disorders¹²⁹⁻¹³³ e.g. in one study a combination of 3 miRNAs (miR-663a, miR-502-3p and miR-206) classified FTD from controls with an accuracy of 84.4%¹²⁹. miRNAs may also act as staging markers e.g. one study showed a difference in two miRNAs (miR-204-5p and miR-632) in CSF between symptomatic and presymptomatic mutation carriers in genetic FTD¹³³.

The future – clinical trials and treatment response

The future of FTD is an increasing number of therapeutic studies and potentially a point in time where most diagnosed patients are entering into clinical trials. It is important to remember that whilst many of these will be disease-modifying, trials of symptomatic treatments will also

continue to be important e.g. improvement in altered eating behaviour [see Box 5]. Discovery of better markers of staging and therapeutic response in particular will be required, and whilst new technologies [Box 2] that allow multiple proteins to be measured at the same time in increasingly sensitive ways, will be important, it will also be imperative to look beyond the fluid biomarker field to consider multimodal combinations of measures that cross biofluids, magnetic resonance imaging, and positron emission tomography, making use of new data science methods, including machine and deep learning. It is likely that such studies will take place within the context of large cohort studies [see Box 6] avoiding the problems of small sample sizes that are inherent to so many of the published papers so far. Such studies will also pave the way for larger -omics studies which have so far been relatively small and focused on proteomics despite initial evidence for abnormalities in metabolomics¹³⁴⁻¹³⁶ and lipidomics¹³⁷⁻¹³⁹ in FTD as well.

Conclusion

The past of FTD biomarkers as described here is a wide range of different markers, some more promising than others, but many examined in small single centre cohorts. The present is the recent introduction of more sensitive blood-based biomarker methods and the availability of larger sample collections from the well-characterized multinational genetic FTD cohorts, with great promise for markers such as NfL and GFAP, and a negative predictive value of p-tau. The future is trials and within this the validation of multiplex biomarker panels targeted at specific pathogenetic forms of FTD, and eventually to individuals, providing a more personalized approach to outcome measures in upcoming trials.

Box 1: Biosamples

Cerebrospinal fluid surrounds the brain and spinal cord, coming into direct contact with the extracellular space. It is therefore the most effective biological fluid to measure biochemical changes in brain tissue. However, in recent years, there has been an increasing focus on biomarkers in *blood (plasma or serum)*, which form a less invasive and more accessible alternative. Unfortunately, studies of blood-based biomarkers involve overcoming a number of challenges¹⁴⁰: firstly, the marker needs to be able to cross the blood-brain barrier and if the marker is nonspecific to the central nervous system, there is a risk of peripheral contamination; secondly, numerous other blood-based proteins and heterophilic antibodies, which are higher in blood than CSF, are likely to interfere with measurements; and finally, pre-analytical factors, such as food intake or diurnal variation, need to be considered as these may be more relevant in blood. Fortunately, recent technological developments, such as Single molecule array (Simoa) technology (detailed further in Box 2), allow for more sensitive assays, eliminating many of these challenges. One other potential way of improving peripheral identification of neuronally-derived biomarkers is through the measurement of proteins within *exosomes*¹⁴¹. These are small extracellular vesicles, released by cells, including within the brain, and able to cross the blood-brain barrier, suggesting that measurement of their content in blood (as well as in CSF) may well represent central nervous system processes¹⁴². Technology is now available to extract neuronal exosomes within blood¹⁴³, making them an important prospect for future studies. Lastly, other body fluids poorly studied as potential sources of biomarkers in FTD are **urine**¹⁴⁴ or **saliva**¹⁴⁵, and future studies would benefit from investigating these further.

Box 2: Measurement techniques

There are several platforms offering assays for biomarker measurement and discovery:

- **ELISA** (enzyme-linked immunosorbent assay) is the classical technique to measure proteins in fluids. In the commonest format, target-specific antibodies bind to the sample proteins and a secondary antibody linked to an enzyme recognise the matched antibodies (a so-called sandwich ELISA). The conjugated enzyme can create a chromogenic or fluorescent reaction when exposed to a chemical substrate, with the amount of antigen present directly correlated to the intensity of the colour change. It is a quantitative technique that has been widely used in the biomarker field, although it usually only allows one analyte per assay and the detection range is inferior to other high-sensitivity techniques (on the pM to nM range).
- **MSD** (Mesoscale Discovery) is a high throughput platform to measure proteins, increasing the sensitivity of conventional ELISAs, measuring the levels of single or multiple targets within a single, small-volume sample. Unlike conventional ELISAs, detection antibodies can be directly conjugated to SULFO-TAG to generate electrochemiluminescent signals that have a voltage-dependent activation.
- **Luminex®** is a high-throughput screening technology (on the picogram scale) that consists of a bead-based technology in which each bead presents a different colour code and each one is conjugated with an antibody against a specific analyte. It can be very useful to develop and measure biomarker panels of up to 80 different analytes from a single microplate well, reducing the sample volume needed. With this platform it is possible to measure not only protein but also RNA and DNA.
- **Simoa®** (Single molecule array) is an ultrasensitive immunoassay in two different versions. The conventional antibody-based ELISA in a planar array format and a bead-based platform in which each antibody-coated bead binds to a single molecule of analyte and then is analysed separately

from the rest, offering a high sensitivity and wide detection range (on the fM to pM scale). The assay format allows multiplexing of up to 11 analytes and provides the possibility to develop home brew assays. A recently described upgrade of the technology might even allow for sub-attomolar quantification¹⁴⁶.

- The **SomaScan® Platform** is based on Slow Off-rate Modified Aptamers. Aptamers are short, single-stranded DNA or RNA (ssDNA or ssRNA) molecules that can selectively bind to a specific target, including proteins, peptides, carbohydrates, small molecules, toxins, and even live cells. In the SomaScan Platform, these aptamers bind to tertiary structures of the targets that are then quantified by standard DNA techniques such as microarrays or qPCR. The platform allows for the creation of a library of specific aptamers with high sensitivity for particular targets (from fM to pM concentrations).
- **Proximity Extension Assay** technology (**Olink®**) consists of matched antibodies with DNA tags that bind to proteins. When matched antibodies come in high proximity, DNA tags will only hybridise when the coupled antibodies match and then the sequence is amplified by qPCR. The platform provides a wide library of matched antibodies with high sensitivity and specificity for the target.
- In the **Single Molecule Counting (SMC)** platform, the antibody-antigen sandwich complexes, originating from either beads or plates, are broken up and only the fluorescently labelled detection antibody is counted one by one using a laser beam that excites the fluorophore. A digital event is counted if the fluorescence reaches above the threshold of the background. At higher concentrations, it is difficult to separate all events and a switch can be made to use the total sum of all emitted photons as readout for the signal, allowing for a high dynamic range (on the fM to pM scale).

- **Mass spectrometry** is usually used for the discovery of new biomarkers but targeted quantitative assays are also available, e.g. through parallel reaction monitoring. It is the most specific technique but it involves long development of each assay and the instruments are expensive and require a high level of expertise. The technology is often used when establishing a reference method where analytical specificity is key, in biomarker discovery projects, or to measure small molecules, such as drugs, lipids and metabolites. Targeted protein biomarker panels are now getting increasingly common as well.

Box 3 Neurofilament light chain – diagnosis, prognosis and staging of FTD

Neurofilaments are intracellular filaments found in the central and peripheral nervous systems. They can be found in different assemblies including neurofilament light chain (NfL), neurofilament medium chain and neurofilament heavy chain (NfH). All of them function as elastic assemblies that help maintain cell shape¹⁴⁷, and in neurons, this action controls axonal diameter, modulating the response to stimuli. When there is neuronal damage or axonal injury, they can leak and be found in the CSF. Of all the neurofilaments, NfL has been the most studied. Initial studies in FTD within CSF showed that NfL was raised in many patients with different phenotypes¹⁴⁸. More recently, the use of an ultrasensitive assay on the Simoa platform has allowed accurate measurement of NfL within blood (with high correlation with CSF concentrations). Studies have shown that concentrations reflect how fast the disease is progressing (i.e. disease intensity)^{149,150,151}, and are a measure of survival in most FTD phenotypes^{152,153} but not all (e.g. svPPA^{154,155}). Diagnostically, whilst concentrations are variable and overlap with other neurodegenerative disorders¹⁵⁶, NfL concentrations are nonetheless higher than in primary psychiatric disorder mimics of FTD¹⁵⁷. Furthermore, concentrations rise sharply just prior to symptom onset in genetic FTD as presymptomatic mutation carriers phenoconvert (Figure 2C)^{152,158}. In summary, the measurement of NfL offers a number of opportunities in the FTD biomarker field. Firstly, as a diagnostic marker, helping to differentiate FTD in the clinical setting from a non-neurodegenerative disorder. Secondly, as a marker of proximity to symptom onset, its baseline measurement is likely to predict progression to clinical symptoms in presymptomatic mutation carriers. Thirdly, its measurement during the symptomatic period provides an indication of how fast the disease is progressing and therefore likely prognosis. Lastly, like in other diseases, the ability to decrease NfL within the context of a disease-modifying trial is likely to be a positive indication of a decrease in the rate of neurodegeneration¹⁵⁹. Fewer studies have investigated NfH: levels are increased¹⁶⁰ in FTD, although its utility seems less than for NfL except when there is associated ALS, where it may serve as a marker of prognosis¹⁶¹ and treatment response¹⁶².

Box 4: Staging of FTD and proximity markers

Unlike in AD, few markers of disease stage have been identified in FTD so far. 'Preclinical' FTD may be defined by the onset of detectable pathological changes, but at present, we have no biomarkers of tau, TDP-43 or FET that might theoretically become abnormal quite a number of years prior to symptom onset. Whilst we do have markers of DPRs in *C9orf72* expansion related disease, further studies of when these become abnormal are required (as it is likely that in this group DPR pathology precedes TDP-43 pathology¹⁶³). 'Prodromal' FTD may be defined by the onset of mild symptoms that do not meet diagnostic criteria i.e. mild behavioural, cognitive (and/or motor) impairment. During or just prior to this stage we may define 'proximity measures' i.e. those identifying a period prior to phenocconversion and for FTD both NfL^{152,158} and GFAP in *GRN* mutation carriers⁸⁹ are candidates for these.

Box 5: Measures of hypothalamic function

Excessive eating and dietary changes are well recognised in FTD, and can be used to differentiate bvFTD from AD^{20,164–166}. Studies investigating eating behaviour have shown altered metabolism^{166–169}, and so studies have begun to focus on molecular measures of appetite, and therefore also the hypothalamus, as it acts as a key control centre in modulating appetite through various highly interconnected nuclei that communicate through neuropeptides^{165,170–172}. Lower levels of ghrelin and cortisol, but higher levels of insulin have been observed in bvFTD compared with controls and AD¹⁷³. In the same study, higher levels of leptin were found in those with marked hyperphagia¹⁷³. These metabolic patterns are consistent with a state of satiety, which suggests the eating disturbances observed in FTD result from loss of inhibitory signals; however, the compensatory hormonal responses cannot reverse these symptoms. The first study investigating CSF agouti-related peptide (AgRP) in FTD, found a 7-fold increase in people with TDP-43 pathology compared to people with tau pathology⁹⁵. A further study also detected increased levels of AgRP in bvFTD and svPPA compared to controls¹⁶⁵, also showing that both AgRP and leptin were predictors of body mass index¹⁶⁵. These findings of elevated AgRP, which stimulates appetite, suggest that neuropeptides may directly be involved in modulating eating behaviour in FTD and promote excessive eating. In a further study, decreased neuropeptide Y (NPY) levels were found in people with FTD compared to controls and patients with ALS¹⁷⁴. They also showed increased levels of leptin and insulin resistance in people with bvFTD and ALS¹⁷⁴, further complicating the picture of metabolic changes underlying eating disturbances in FTD. Few metabolic studies have focused on specific forms of FTD so far; however, in one study focused on *GRN*-related FTD, serum C-peptide, resistin and ghrelin were all increased¹⁷⁵. Lastly, hypothalamic proteins have been studied in relation to sleep in FTD, with CSF orexin levels being correlated to daytime somnolence¹⁷⁶ in one study, and plasma orexin being lower in people with FTD compared with controls in another¹⁷⁷.

Box 6: FTD cohorts

As FTD is a rare disease with multiple phenotypes and pathogenetic causes, a substantial number of prior biomarker studies have involved relatively small sample sizes, reducing the power, and likelihood of finding abnormalities. In recent years, however, larger deeply phenotyped cohorts have been developed that have facilitated biomarker studies of increased size. In genetic FTD, these include the Genetic FTD Initiative (GENFI: www.genfi.org)¹⁷⁸ in Europe and Eastern Canada, and the ARTFL/LEFFFTDS (now ALLFTD: <https://www.allftd.org>) cohort in the US and Western Canada^{179,180} who collaborate through the FTD Prevention Initiative (www.thefpi.org)¹⁸¹. The ALLFTD cohort also includes sporadic FTD, and whilst there are no large multinational cohorts in Europe, large studies of FTD with biomarker analyses include the German FTLD consortium¹⁸² and DZNE FTD DESCRIBE cohort¹⁸³. Specific atypical parkinsonian cohorts include the UK PROSPECT study¹⁸⁴ and the US 4RTNI cohort¹⁸⁵.

Table 2: Lysosomal markers

LAMP1 (lysosomal-associated membrane protein 1); ↑ (increased levels), ↓ (decreased levels), - (unchanged levels) all compared to controls; P (presymptomatic), S (symptomatic); Green (in blood and CSF), Blue (in CSF), Red (in blood), Yellow (in neuron derived exosomes from plasma).

Fluid biomarkers	Biological function	Unspecified FTD	PSP	FTD-GRN		FTD-C9orf72		FTD-MAPT		Ref.
				P	S	P	S	P	S	
LAMP1	Glycoprotein involved in regulation of lysosomal function	-	-							109, 110
Cathepsin D	Protease involved in degrading proteins such as PGRN in the lysosome	↑								109
α-Mannosidase	Lysosomal hydrolase	↓								112
Lysozyme	Innate immunity enzyme		↑							110

DOPAC	Dopamine metabolite	↓									126
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FIGURE LEGENDS

Figure 1: Clinical-pathological-genetic correlations in the FTD spectrum. The innermost part of the circle depicts the genetic causes of FTD. The middle part depicts the different pathological causes: PiD = Pick's disease, PSP = progressive supranuclear palsy, CBD = corticobasal degeneration, MAPT = pathology-associated with MAPT mutations, GGT = globular glial tauopathy, UPS = ubiquitin-proteasome system, BIBD = basophilic inclusion body disease, NIFID = neuronal intermediate filament inclusion disease, aFTLNU = atypical FTLD with ubiquitin inclusions. The outermost part of the circle represents the clinical diagnoses associated with each pathology – the largest font being the most common syndrome, the medium font being syndromes less commonly seen, and the smallest font being rare phenotypes.

Figure 2: Key biomarkers in FTD – A. Plasma progranulin levels in *GRN* mutation carriers (from Galimberti et al, 2018³⁹); **B. CSF poly(GP) dipeptide repeat (DPR) protein levels in *C9orf72* mutation carriers** (from Meeter et al, 2018⁵¹); **C. Longitudinal serum neurofilament light chain (NfL) protein levels in genetic FTD** (from van der Ende et al, 2019¹⁵⁸).

Figure 3: Biological pathways of progranulin. This diagram depicts biological interactions of progranulin inside and outside the cell. PGRN (progranulin), SLPI (serine leukocyte protease inhibitor), PSAP (prosaposin), TNFR (tumour necrosis factor receptor), Eph2 (Ephrin receptor 2).

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Disclosures

HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. The other authors declare no conflicts of interest.

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