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# Biomarkers in Frontotemporal Lobar Degenerations – Progress and Challenges

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## Abstract

Neuronal and glial changes associated with tau, TAR DNA binding protein of ~43 kD (TDP-43), and fused in sarcoma (FUS) together constitute the pathologic spectrum of frontotemporal lobar degeneration (FTLD). Most patients with FTLD present with prominent behavior or language changes, sometimes accompanied by extrapyramidal symptoms or motor neuron disease. Identification of FTLD patients with mutations in genes for tau, TDP-43, and FUS lends strong support for their pathogenic roles in FTLD, and elucidation of their dysfunction will pave the way for development of substrate specific therapy. However, there remains no reliable biomarker for early detection of FTLD or prediction of underlying FTLD pathologic change. Clinical syndromes usually reflects the earliest affected brain regions where atrophy can be visualized on structural MRI, but neither clinical nor structural imaging-based biomarkers has been accurately correlated with underlying pathology on the individual patient level. Biochemical markers in the cerebrospinal fluid (CSF) have also been investigated in FTLD and related disorders, including amyotrophic lateral sclerosis (ALS) and progressive supranuclear palsy (PSP). However, their accuracy and pathologic significance need to be confirmed in future multi-center studies. Here we review the progress made in FTLD biomarkers, including clinical phenotype/feature characterization, neuropsychological analysis, CSF and plasma analytes, and patterns of brain atrophy and network dysfunction detectable on brain imaging. Given the pathologic overlap of FTLD with ALS and PSP, collaboration with specialists in those fields will be essential in the translation of promising FTLD biomarkers into clinical practice.

### Keywords

Biomarker; diagnosis; frontotemporal dementia; tau; tauopathy; TDP-43

## 1. Introduction

Frontotemporal lobar degeneration (FTLD) represents a group of clinically and pathologically heterogeneous disorders, with an estimated prevalence of 3-15/100,000 in



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adults under the age of 65.(Ratnavalli *et al*., 2002; Rosso *et al*., 2003) Traditionally, clinical descriptions of FTLD have largely been restricted to patients with prominent behavior or language disorders. With evolving terminology, these patients have been referred to as having frontotemporal dementia (FTD),(Neary *et al*., 1998) behavior variant of FTD (bv-FTD),(McKhann *et al*., 2001; Rascovsky *et al*., 2007a) primary progressive aphasia (PPA), (Grossman, 2010; Mesulam, 1982, 2001) or language variant of FTD (lv-FTD).(McKhann *et al*., 2001) The rendering of a specific syndromic diagnosis can be challenging due to the sometimes mixed nature of language and behavioral symptoms in these patients, which is only made more difficult with the recognition that the cognitive FTLD patients can develop additional symptoms in keeping with motor neuron disease or parkinsonian disorders. (Josephs, 2008) The emergence of these non-cognitive symptoms should not come as a surprise, as work in motor neuron disease and movement disorders has independently identified cognitive symptoms in patients with established amyotrophic lateral sclerosis (ALS),(Hu *et al*., 2009b; Lomen-Hoerth *et al*., 2002; Strong *et al*., 2003) corticobasal degeneration (CBD),(Bak *et al*., 2005; Kertesz *et al*., 2000; Murray *et al*., 2007) and progressive supranuclear palsy (PSP)(Bak *et al*., 2005; Esmonde *et al*., 1996; Kertesz and McMonagle, 2010) to be similar to those seen in FTLD patients with cognitive-only or cognitive-predominant features. The behavior-language-motor connection in FTLD patients is further strengthened by the observation that patients belonging to the same clinical spectrum tend to share the same pathologic substrate: abnormal accumulation of hyperphosphorylated tau in those with cognitive symptoms and CBD/PSP,(Josephs *et al*., 2006b; Murray *et al*., 2007) and abnormal accumulation of hyperphosphorylated and ubiquitinated TAR DNA binding protein of 43 kD (TDP-43) in those with cognitive symptoms and ALS.(Hu *et al*., 2009b; Josephs *et al*., 2006b; Neumann *et al*., 2006) FTLD-TDP and FTLD-Tau each contains multiple subtypes, including subtyping according to patterns of TDP-immunoreactive lesions in FTLD-TDP(Mackenzie *et al*., 2009; Neumann *et al*., 2006) and according to predominant tau isoform inclusion and/or affected cellular (neuronal vs. glial) population.(Mackenzie *et al*., 2009) Even though details on how the different subtypes differ biochemically and clinically from each other within FTLD-TDP or FTLD-Tau still need clarification, the diagnostic groupings of FTLD-TDP and FTLD-Tau account for the majority of patients who present with prominent behavior, language, or motor symptoms who do not have atypical Alzheimer's disease (AD) or dementia with Lewy bodies (DLB), while a small proportion of FTLD patients without characteristic Tau or TDP-43 immunoreactive changes have pathology associated with fused in sarcoma (FUS).(Urwin *et al*., 2010)

The relatively recent identification of one protein (TDP-43 or Tau) as the common denominator in a spectrum disorder raises the possibility that the characteristic protein is a late-stage epiphenomenon that likely does not carry pathogenic significance. Evidence against this has come from genetic cases of FTLD in whom the *TARDBP* (Benajiba *et al*., 2009; Borroni *et al*., 2009; Corrado *et al*., 2009; Kabashi *et al*., 2008; Kuhnlein *et al*., 2008; Sreedharan *et al*., 2008), *MAPT*(Hutton, 2001), or *FUS*(Kwiatkowski *et al*., 2009; Vance *et al*., 2009) gene is itself mutated. Such cases of FTLD often have cognitive PLUS additional symptoms, such as ALS in families with *TARDBP* mutations and prominent parkinsonism in patients with *MAPT* mutations (otherwise referred to as frontotemporal dementia with parkinsonism linked to chromosome 17, or FTDP-17). FTLD cases with mutations in these or other genes invariably have FTLD pathology corresponding to the mutation, although such straightforward clinicopathologic correlation does not exist for most of the sporadic FTLD cases without known mutations. In addition, for reasons that remain enigmatic, familial FTLD caused by mutations in the progranulin gene (*PGRN*) have TDP-43 inclusions as the underlying neuropathology.(Mackenzie, 2007; Mackenzie *et al*., 2006) Thus, in elucidating disease mechanisms that link abnormal protein deposition to progressive dementing syndromes with hopes of developing substrate-specific therapies

targeting tau or TDP-43, accurate prediction of underlying FTLD pathology is essential for human studies similar to those ongoing in AD(Petersen *et al*., ; Shaw *et al*., 2009; Trojanowski *et al*., 2010b) or Parkinson's disease (PD)(MJFF, 2010) including but beyond those cases with known mutations. Such a search for pathologic predictors, or diagnostic biomarkers, in FTLD has followed more established directions laid out in AD biomarker research, although no putative FTLD biomarker (for TDP or tau) is currently as reliable as cerebrospinal fluid (CSF) levels of pathology-related proteins(Shaw *et al*., 2007; Shaw *et al*., 2009) or even hippocampal volume(Schuff *et al*., 2009) in AD. Thus, to facilitate our efforts and those of others to confirm and explore the utility of single and combinatorial biomarkers for FTLD diagnosis and prognosis, here we review the recent advances in FTLD biomarker development in terms of clinical, biochemical, and imaging based strategies. As there are few studies on FUS-related biomarkers,(Josephs *et al*., 2010b) we will focus primarily on biomarkers related to FTLD-TDP and FLTD-Tau.

## 2. Clinical FTLD biomarkers

Several well-executed surveys on the pathologic substrates for cognitive forms of FTLD have led to generalization on the correlation between clinical syndromes (or phenotypes) and pathologic substrate.(Forman *et al*., 2006; Hodges *et al*., 2004; Josephs *et al*., 2006b; Kertesz *et al*., 2005) Cases usually come from tertiary referral centers with expertise in cognitive forms of FTLD and associated motor neuron/parkinsonian disorders, although the composition of the autopsy cohort can significantly differ due to referral bias among other reasons. Bias aside, these studies showed a general pathologic predilection for certain subtypes of clinical syndromes (Table 1): patients with progressive non-fluent aphasia (PNFA, also referred to as agrammatic/non-fluent form of PPA) are more likely to have FTLD-Tau than FTLD-TDP, patients with semantic dementia (SD or SemD) or the semantic variant (SV) of PPA often have FTLD-TDP instead of FTLD-Tau, and patients with bv-FTD are as likely to have FTLD-TDP as the cause of their clinical symptoms as FLTD-Tau. While these findings continue to be replicated in most independent clinicopathologic series, it is often challenging to translate these population-level probabilities into clinical practice for the individual patient. For example, while FTLD-Tau is the most common cause for PNFA, atypical AD and FTLD-TDP can also account for significant proportions of patients with agrammatic/non-fluent speech.(Alladi *et al*., 2007; Forman *et al*., 2006; Hu *et al*., 2010e; Mesulam *et al*., 2008) Further characterization of their non-fluency through detailed language examinations can identify patients who are more likely to have underlying pathology of AD rather than a FTLD,(Gorno-Tempini *et al*., 2008; Hu *et al*., 2010e) but such strategy creates another category of heterogeneous pathology.(Mesulam *et al*., 2008) Importantly, while syndrome-based diagnosis is crucial in the understanding of pathology-behavior relationship,(Gunawardena *et al*., 2010) assignment of a clinical syndrome does not seem to improve the overall diagnostic accuracy when it comes to pathologic prediction.

Beyond cognitive forms of FTLD, similar diagnostic challenges have been plaguing clinicopathologic work of CBD which is often viewed as a FTLD spectrum disorder. CBD, as a pathologic diagnosis,(Dickson *et al*., 2002) was originally hoped to have strong correlations with the clinical syndrome carrying the same name.(Boeve *et al*., 2003; Litvan *et al*., 1996) However, even when strict diagnostic criteria are applied, clinical prediction for CBD is poorly sensitive and specific for pathologic changes diagnostic for CBD.(Boeve *et al*., 1999) In fact, CBD may represent a minor cause of clinically diagnosed cases of corticobasal syndrome (CBS) with a recent study showing a positive predictive value under 25% for the clinical diagnosis.(Ling *et al*., 2010) These findings have led to a recent re-evaluation of diagnostic criteria for CBD, and it remains unclear if a standard set of clinical criteria can be successfully formulated in spectrum disorders such as CBD. This is best illustrated by examples in the most common form of tau-negative FTLD, i.e. FTLD-TDP. In

FTLD-TDP, patients can develop cognitive symptoms of FTLD, motor neuron disease (ALS or primary lateral sclerosis), or both.(Geser *et al*., 2008; Josephs *et al*., 2006b; Lomen-Hoerth *et al*., 2002; Neumann *et al*., 2006) In patients with cognitive only or cognitive predominant FTLD, strict criteria for ALS (such as modified El Escorial criteria)(Brooks *et al*., 2000) will not be met for nearly all bv-FTD and SD, including sometimes in cases with pathologic motor neuron involvement.(Josephs *et al*., 2006a) Similarly, in patients with ALS in whom up to 50% may have minor cognitive symptoms (including 15% with dementia,(Hu *et al*., 2009b; Lomen-Hoerth *et al*., 2002), severity of dementia or aphasia may be difficult to determine due to functional impairments from motor deficits.(Geser *et al*., 2008) Therefore, while additional symptoms in keeping with ALS (such as single limb involvement, prominent fasciculations) or CBD/PSP (apraxia, supranuclear palsy) may be very useful in the prediction of underlying FTLD pathology, a criteria-based approach may leave many patients with otherwise predictable pathology in a category of diagnostic uncertainty.

An extension of feature-based characterization in predicting underlying FTLD pathology involves detailed neuropsychological analysis of patients.(Libon *et al*., 2007b) While neuropsychological evaluation is commonplace in patients with mild cognitive impairment (MCI) or early AD, (Loewenstein *et al*., 2006; Petersen *et al*., 2010) its use in FTLD is more variable(Collette *et al*., 2007; Hutchinson and Mathias, 2007; Libon *et al*., 2007a; Libon *et al*., 2007b; Rogers *et al*., 2006; Rosen *et al*., 2004) and few studies have incorporated neuropathologic evaluation as the “gold standard” in pathologic prediction.(Grossman *et al*., 2008; Rascovsky *et al*., 2007b) The development and validation of a neuropsychological biomarker (for FTLD-TDP or FTLD-Tau) can be quite discouraging for multiple reasons. First, multiple cognitive domains are often involved in clinical syndromes involving behavior or language impairments (for example, naming and speech praxis in non-fluent speech), and limited standardized batteries are available for these functions in isolation. Second, the main differences between two pathologic groups can be biased by uneven distribution of certain syndromes in each pathologic group. For example, if the FTLD-TDP group has a high number of SD cases, confrontation naming can emerge as a predictor for FTLD-TDP even though confrontation naming is often preserved in bv-FTD due to FTLD-TDP and SD cases account for a small proportion of all FTLD-TDP cases. (Grossman *et al*., 2007; Grossman *et al*., 2004) Lastly, multiple autopsy-confirmed studies have shown that patients with the same clinical phenotype can have very similar neuropsychological profiles in terms of absolute impairments that reflect the characteristic deficits for the clinical diagnosis (for example, impairment in praxis or visual-spatial function in CBS, or fluency in PNFA)(Hu *et al*., 2010e; Hu *et al*., 2009a; Vanvoorst *et al*., 2008). While these studies may be discouraging, two observations have revived interests in the development of a neuropsychological biomarker to predict underlying FTLD pathology. First, in one series of autopsy-confirmed cases of FTLD-TDP and FTLD-Tau, it appeared that the relative performance of paired neuropsychological tests can be related to the underlying FTLD pathology: FTLD-TDP patients had more impaired confrontation naming and category fluency than visual spatial function, while FTLD-Tau patients have the opposite pattern. (Grossman *et al*., 2008) Second, work on structural and functional brain imaging has revealed possible networks of distant brain regions that are preferentially affected by FTLDs.(Listerud *et al*., 2009; Seeley *et al*., 2009) When examined together, these two observations raise the possibility that there exist regions in the brain commonly affected by FTLD-TDP or FTLD-Tau irrespective of the clinical phenotype, and neuropsychological evaluation of network-level brain functions can allow for the differentiation between FTLD-TDP and FTLD-Tau.(Listerud *et al*., 2009) We recently demonstrated the potential of such a comparison when we examined the relative performance on letter-guided fluency and confrontation naming in patients with non-fluent speech and autopsy or CSF AD biomarker confirmation.(Hu *et al*., 2010e) Whereas direct comparison of cognitive performance did not

reveal any difference between those with FTLD vs. AD, we were able to predict underlying AD pathology based on worse relative performance in confrontation naming compared to letter-guided fluency with moderate accuracy. This relative pattern of impairment was subsequently found in patients with CBS due to FTLD or AD,(Gross *et al*., 2010) which demonstrates preliminary evidence for the syndrome-independent nature of such a neuropsychological biomarker. While the relative performance of paired neuropsychological subtests has not been prospectively tested in FTLD, better characterization of jointly impaired cognitive domains may provide better understanding of FTLD pathology-specific large scale brain networks.

While a phenotype-based diagnostic algorithm has limited sensitivity or specificity for FTLD pathologic prediction, useful information such as prognosis can still be gleaned from a syndromic diagnosis.(Xiong *et al*., 2010) For example, patients with SD and FTLD-TDP often have longer survival and lower chances of developing motor neuron symptoms than FTLD-TDP patients presenting with bv-FTD.(Hodges *et al*., 2010; Seeley *et al*., 2005) These differences may reflect the specific FTLD subtyping, as neurites immunoreactive to TDP-43 are more common in SD than bv-FTD,(Grossman *et al*., 2007; Hodges *et al*., 2010). Similarly, survival in patients with ALS (with or without cognitive impairment) is often shorter than those with bv-FTD due to FTLD-TDP, and there continues to be speculation whether prognosis is determined by pathology, clinical syndrome, or both. Given all the possible combinations of clinical syndrome and FTLD pathology, we propose that FTLD patients be not labeled by their presenting phenotype alone. Instead, each patient should be classified according to their main pathologic substrate, possibly through biochemical biomarkers for AD and FTLD, other investigations suggestive of pathology (such as abnormal electromyography for co-existing subclinical ALS), or future biomarker/technology as they become available, along with their presenting phenotype for monitoring of disease progression.

## 3. Biochemical FTLD biomarkers

A limited number of biochemical biomarkers have been investigated in cognitive forms of FTLD (Table 2), although many have been identified in related disorders such as ALS and PSP. The earliest attempts to predict underlying FTLD pathology followed strategies proven successful in AD. As tau hyperphosphorylation is a common feature between AD and FTLD-Tau, tau-related AD biomarkers – elevated levels of total tau and hyperphosphorylated tau at threonine 181 (p-tau$_{181}$) – were examined as potential FTLD biomarkers. In a group of clinically characterized FTLD patients, p-tau$_{181}$ levels were decreased in these patients compared to control subjects and AD patients.(Vanmechelen *et al*., 2000) In another group of FTLD patients with detailed neuropathologic analysis, normal levels of CSF tau and p-tau$_{181}$ levels were again found in patients with FTLD-Tau compared with control subjects, and there was even a trend that total tau levels were decreased in FTLD-Tau cases compared to tau-negative FTLD cases.(Bian *et al*., 2008) When this was expanded to a larger living cohort (no autopsy confirmation) divided according to likelihood of FTLD-Tau vs. FTLD-TDP based on clinical syndromic diagnosis, the trend persisted but remained non-significant.(Hu & Grossman, unpublished data) Thus, among patients with a FTLD-related clinical syndrome, a normal CSF AD biomarker profile is suggestive of underlying FTLD by ruling out AD pathology. While we and others have employed such approaches to determine group-level differences in hopes of a more homogeneous cohort of FTLD patients than patients classified by clinical syndromes only,(Hu *et al*., 2010e; Hu *et al*., 2010f) the occasional detection of altered AD biomarker levels in CSF of patients with clinically unambiguous ALS or genetic cases of FTLD strongly reflects the presence of AD co-pathology in some FTLD cases. Thus, a biomarker positively predictive of FTLD (rather than the absence of a positive biomarker for AD) is essential in a CSF diagnostic algorithm

of FTLD. Along that line, levels of structural proteins such as neurofilament heavy and light chains have been found to be elevated in FTLD compared to AD and control subjects at the group level,(Petzold *et al*., 2007) but its ability to distinguish between potential etiologies at the individual levels remains uncertain.

Following the identification of TDP-43 as a main ubiquitinated protein in FTLD-TDP, TDP-43 itself has become a target of biomarker discovery. In plasma samples from clinically characterized patients, about half of patients with bv-FTD and a quarter of patients with AD have elevated TDP-43 levels but with significant overlap between the two groups. (Foulds *et al*., 2008) In clinically defined patients with ALS (with and without dementia), CSF levels of TDP-43 were also elevated at the group level with significant overlap with neurologically healthy control subjects.(Kasai *et al*., 2009; Steinacker *et al*., 2008) The low absolute levels of TDP-43 detected also raised questions regarding assay robustness, sensitivity and specificity.(Kasai *et al*., 2009) To-date, it remains unclear whether plasma or CSF levels of total TDP-43 differ between cases with autopsy confirmation, although highly sensitive measures for phosphorylated species of TDP-43 may yet yield useful findings.

As a major cause for familial FTLD-TDP, progranulin levels have been directly measured in patients with clinical syndromes associated with FTLD as *PGRN* mutations results in a protein haploinsufficiency.(Baker *et al*., 2006; Gass *et al*., 2006) In familial FTLD cases with *PGRN* mutations, plasma progranulin levels were decreased compared to control subjects.(Finch *et al*., 2009) This finding has been further extended to cognitively impaired patients homozygous for the T allele of PGRN rs5848, a group of subjects suspected of having increased risks of developing FTLD-TDP.(Hsiung *et al*., 2010; Rademakers *et al*., 2008) However, while plasma progranulin levels are decreased in FTLD patients and asymptomatic family members carrying the mutation, progranulin levels in patients with FTLD-related disorders without *PGRN* mutations remain indistinguishable from control subjects,(Finch *et al*., 2009) limiting the application of this biomarker in most cases of FTLD-TDP.

We and others have taken more unbiased approaches towards novel biomarker discovery in FTLD (Table 2). Using small groups of clinically characterized FTLD patients without neuropathologic confirmation, putative biomarkers for FTLD have been identified, including granin-like neuroendocrine precursor, apoliprotein E, pigment epithelium derived growth factor, retinol-binding protein, and haptoglobin in one study (with RBP, apoE, and haptoglobin also altered in AD);(Davidsson *et al*., 2002a; Davidsson *et al*., 2002b) neurosecretory VGF, cystatin C, transthyretin, and chromogranin B.(Ruetschi *et al*., 2005) Among these, retinol-binding protein, apoliprotein E, haptoglobin, VGF, and transthyretin were also altered in AD in similar directions, even though VGF was identified in a separate study to be altered in ALS.(Pasinetti *et al*., 2006) Chromogranin B is a potential marker for FTLD-TDP as it is associated with increased risk for ALS, (Gros-Louis *et al*., 2009) and cystatin C showed the most promise in being specific to FTLD (or a FTLD subtype) with an opposite direction of change from AD patients.(Ruetschi *et al*., 2005) As part of a larger targeted proteomic study,(Hu *et al*., 2010b) we measured CSF levels of 151 proteins in multiplexed immunoassays in 23 patients with autopsy-confirmed FTLD-TDP or FTLD-Tau, along with 80 living patients with a clinical syndrome suggestive of underlying FTLD pathology (bv-FTD, PPA, CBS) whose CSF levels of AD-biomarkers are not suggestive of AD pathology. (Hu *et al*., 2010d) Similar to the prior study, we did not see a significant difference in total tau levels between autopsy-confirmed cases of FTLD-TDP and FTLD-Tau despite a similar trend. At the same time, levels of a number of proteins differed between the two main pathologic FTLD groups, including neuropeptides (agouti-related peptide, adrenocorticotropic hormone), members of the apoptotic pathways (Fas, TRAIL-R3), inflammatory chemokines (macrophage derived chemokine, IL-17, IL-23), structural

protein (S100b), and apolipoprotein B. Whereas patterns of tau and Aβ42 change in AD likely reflect the early pathogenic processes (soluble tau release and Aβ42 deposition), some alterations we observed in FTLD may instead reflect downstream effects of disease. This hypothesis is based on the observation that many of these altered peptides derive from similar biological pathways, such as the agouti-related peptide pathway (AgRP, ACTH) and the IL-17 releasing T-cell pathway (IL-17, IL-23). Using random forests analysis, we were able to achieve moderate sensitivity (86%) and specificity (78%) in the distinction between FTLD-TDP and FTLD-Tau cases. We were also able to classify patients with clinical FTLD syndromes into those likely to have FTLD-TDP or FTLD-Tau, with a trend that is consistent with the probabilistic model from previous clinicopathologic studies (SD having the highest percentage of patients predicted to have FTLD-TDP, and PNFA and CBS having the smallest percentage of patients predicted to have FTLD-TDP). While this panel of diagnostic biomarkers awaits validation in a larger cohort to be recruited and characterized in a multi-center design to begin in 2011, this panel perhaps represents a more mature CSF-based diagnostic biomarker combination for pathologic FTLD subtyping. If successful, plasma-based biomarkers to distinguish between FTLD-TDP and FTLD-Tau can then be developed using patients with CSF suggestive of one or the other FTLD subtype.

CSF biomarkers have also been examined in disorders related to FTLD-Tau (PSP) or FTLD-TDP (ALS). There are fewer studies of CSF biomarkers for PSP, possibly due to the relatively high clinical diagnostic accuracy for PSP compared to other FTLD spectrum disorders.(Josephs and Dickson, 2003; Josephs *et al*., 2006b; Litvan *et al*., 1996) Among available studies, one initially promising biomarker in PSP, complement factor 4d, was also found to be elevated in ALS.(Tsuboi and Yamada, 1994; Yamada *et al*., 1994) A subsequent study on PSP (including 21 clinical PSP and 20 CBS cases) showed a decreased ratio of the truncated form of tau to full length tau in PSP only (but not in CBS).(Borroni *et al*., 2008) This and FTLD-Tau. As discussed above, IL-17 is released by T-cells whose differentiation from immature T-cells depended on IL-23, and paralleled changes in IL-17 and IL-23 in CSF of FTLD-TDP strongly suggests this to be a pathway likely common to the FTLD-ALS spectrum of TDP-43 proteinopathy. In terms of MCP-1, its levels significantly correlated with Fas levels in the CSF which differed between the two main FTLD subtypes.(Hu *et al*., 2010d) Thus, similar to what we observed in a targeted proteomic AD biomarker study,(Hu *et al*., 2010c) certain diagnostic analytes (biomarkers) may serve as proxy for pathways specifically altered in one or more types of neurodegenerative disorders. Comparison of different biomarker studies should then incorporate pathway analysis for proteins of known function for agreement across studies. Furthermore, changes in biologically active processes or pathways – suggested by parallel changes in analytes from the same pathways – may complement pathologic prediction based purely on combinations of functionally unrelated analytes.

Unbiased evaluation of total proteomes from model systems over-expressing TDP-43 or human tissues has also identified potential biomarkers for FTLD. In an *in vitro* model expressing TDP-43, two clusters of proteins – those involved in nuclear RNA splicing and those involved in cytoplasmic translation initiation and elongation – were found to be interacting directly with TDP-43.(Freibaum *et al*., 2010) Some of these proteins have been implicated in human leukoencephalopathies, and may represent the missing link between abnormal TDP-43 accumulation and aspects of large scale brain dysfunction. In another study using post-mortem human brain tissues, direct comparison of 10,000 proteins using mass spectrometry revealed over 200 proteins that differed in levels between FTLD-TDP and FTLD-Tau (unpublished data, Gozal YM, Seyfriend NT, et al.). The identification of these proteins will undoubtedly improve our understanding of the pathogenic processes involved in FTLD-TDP and FTLD-Tau. Some cytoplasmic proteins may also be released into the CSF during early neuronal dysfunction or upon yielded a sensitivity of 87% and

specificity of 86% for the CSF diagnosis of PSP. However, as PSP is a common pathologic cause for clinically diagnosed cases of bv-FTD and CBS,(Forman *et al*., 2006; Josephs *et al*., 2006b) this finding may reflect differential neuroanatomic involvement in motor-predominant forms of PSP rather than a molecular signature of PSP pathology, and this finding was not replicated in another independent cohort of PSP subjects.(Kuiperij and Verbeek, 2010) Another promising biomarker may be CSF orexin, as its levels were found to be decreased in clinical cases of both PSP and CBS compared to control subjects and patients with PD,(Yasui *et al*., 2006) and no different between ALS patients and control subjects.(Van Rooij *et al*., 2009) While orexin levels have not been examined directly in patients with more cognitive-predominant forms of FTLD-TDP or FLTD-Tau, it likely deserves attention in follow-up studies given the paucity of potential biomarkers for tauopathies.

In contrast to PSP, a larger numbers of potential CSF biomarkers have been identified for ALS, including inflammatory proteins (GM-CSF,(Mitchell *et al*., 2009) G-CSF,(Mitchell *et al*., 2009) MCP-1,(Kuhle *et al*., 2009; Mitchell *et al*., 2009) MIP-1a/b,(Mitchell *et al*., 2009) interferon γ, IL-2, IL-6, IL-8, IL-10, IL-15, and IL-17(Kuhle *et al*., 2009; Mitchell *et al*., 2009)), axonal structural proteins (neurofilament light chain(Zetterberg *et al*., 2007)), growth factors (FGF basic protein and VEGF(Mitchell *et al*., 2009)), cystatin C,(Pasinetti *et al*., 2006) insulin-like growth factor 1,(Bilic *et al*., 2006) erythropoietin,(Brettschneider *et al*., 2006) and angiotensin II.(Kawajiri *et al*., 2009) Few of these analytes have been tested in a multi-group basis to include other neurodegenerative disorders such as AD, PD, or DLB, and thus their specificity in predicting TDP-43 proteinopathy remains uncertain. At the same time, some interesting trends emerged when we analyzed together findings from multiple proteomic studies of clinical FTD or pathologic FTLD cases. Among potential TDP-43 biomarkers identified from ALS cohorts, IL-17 and to a lesser degree MCP-1 were found to differ between FTLD-TDP neuronal death to serve as useful biomarkers. Alternatively, direct unbiased proteomic characterization of CSF from patients with known FTLD-TDP (such as ALS with dementia) or FTLD-Tau (such as genetically confirmed cases of FTDP-17) can yield practical CSF biomarkers whose pathologic significance may be less well characterized. The potential utility of such approaches has been demonstrated in animal and human models of familial ALS which yielded galectin-3 as a potential biomarker in ALS,(Zhou *et al*., 2010b) and may complement targeted proteomic approaches for soluble CSF proteins without an insoluble brain component.

While promising, the characterization of biochemical FTLD biomarkers – identified through hypothesis driven, targeted proteomic, or unbiased proteomic studies – should follow procedures similar to those used in the validation and standardization of AD CSF biomarkers for investigators to realize these potential biomarkers' clinical application. (Bjerke *et al*., 2010; Trojanowski *et al*., 2010b) For each analyte or analyte combination, these include determining the effect of collection tube material,(Andreasen *et al*., 1999) post-lumbar puncture centrifugation,(Bjerke *et al*., 2010) storage temperature (room temperature, 4°C, −20°C, −80°C),(Bjerke *et al*., 2010; Mattsson *et al*., 2009) repeated freeze-thawing cycles, immunoassay specificity and reproducibility within and across assay runs (Trojanowski *et al*., 2010b) in addition to factors including age, gender, and genetic influences (such as TMEM106b genotype).(Van Deerlin *et al*., 2010; Vass *et al*., 2010) Beyond AD, such effort has begun to take place in ALS,(Wuolikainen *et al*., 2009) but not in FTLD itself. As we and our collaborators aim to validate the robustness, sensitivity, and specificity of immunoassays for promising CSF-based FTLD biomarkers, these factors must be addressed empirically. Specifically, a multi-center standardization effort will be necessary for assay reproducibility, preferably using aliquots from pooled human samples from subjects with different neurodegenerative disorders. In the multi-center Alzheimer's Disease Neuroimaging Initiative (ADNI), such work involving seven centers showed

coefficients of variation (CVs) of 5.3% for CSF Aβ1-42, 6.7% for t-tau, and 10.8% for p-tau$_{181}$ within centers; and 17.9% for Aβ42, 13.1% for t-tau, and 14.6% for p-tau$_{181}$ across centers.(Shaw *et al*., 2011) In the world wide multicenter standardization effort, inter-center CVs were 21% for Aβ1-42, 15% for t-tau, and 9% for p-tau.(Verwey *et al*., 2009) While system-based standardization efforts are underway in multiple collaborative studies to further reduce these CVs,(Mattsson *et al*., 2010; Verwey *et al*., 2009) values shown from the seven-center ADNI round robin set the benchmark for biomarker assay reproducibility. As summarized recently,(Poste, 2011) assay standardization is especially important as biochemical markers become routinely used as entry criteria or end points for substrate-specific therapeutic trials. As we and others have discovered, multiple pre-analytical and analytical factors can affect the reproducibility of immunoassays for candidate biomarkers, including freeze-thawing cycles, thawing condition (time, room temperature vs. 4°C), extent of handling (including vortexing and centrifugation), strict adherence to the methodologic protocol, dilutional nonlinearity, pipetting equipment and technique, and incubation time, temperature, and buffer.(Mattsson *et al*., 2010; Shaw *et al*., 2011) While some of these factors may be chosen out of convenience, an empirical approach may be necessary to identify reproducible biomarker assays for translation into clinical use.

## 4. Imaging FTLD biomarkers

Early work in imaging studies of FTLD began after the observation that patients with bv-FTD often have prominent atrophy in the frontal or temporal lobar regions. This is thought to be sufficiently distinct from AD to be in clinical use as a practical predictor of FTLD-related dementias. However, clinicopathologic studies have subsequently shown that while such differences can be consistently demonstrated on the group level, it often is unreliable on an individual level for syndromic or pathologic prediction even by experienced radiologists.(Mendez *et al*., 2007; Suarez *et al*., 2009) This may be due to inclusion of slowly progressive forms of FTD,(Davies *et al*., 2006) the occasional finding of no obvious atrophy on MRI,(Kipps *et al*., 2007; Koedam *et al*., 2010) or the overlap between atrophy in FTLD and atrophy in normal aging.(Chow *et al*., 2008) Thus, there has been escalating effort to identify a more reliable imaging measure of FTLD pathology using available imaging modalities beyond visual evidence of frontotemporal atrophy.

Patterns of structural atrophy in FTLD have been examined both in terms of clinical syndromes and pathologic substrates. Along syndromic divisions, atrophy is generally observed in regions associated with the most prominent clinical feature, such as atrophy in the right dorsolateral prefrontal cortex,(Rosen *et al*., 2002a) anterior cingulate cortex, and insula in bv-FTD (Table 3). Certain behavioral characteristics common in bv-FTD can be referred to these regions, such as disinhibition with orbitofrontal and right medial temporal limbic structure atrophy,(Zamboni *et al*., 2008) apathy with dorso-lateral pre-frontal atrophy (Zamboni *et al*., 2008), and poor emotional comprehension with right amygdala and orbitofrontal atrophy. (Rosen *et al*., 2002b) At the same time, frontal atrophy is often found in cognitively normal control subjects, and right frontal lobe atrophy may lack sufficient specificity for bv-FTD.(Chow *et al*., 2008) Similar patterns of group-level atrophy along clinical FTLD syndromes have been reported, including left or bilateral anterior temporal atrophy in SD, left-perisylvian region for PNFA, left temporal parietal junction for logopenic progressive aphasia (LPA),(Gorno-Tempini *et al*., 2008; Hu *et al*., 2010e; Mesulam *et al*., 2008) right or bilateral parietal atrophy in CBS,(Josephs *et al*., 2004) and brainstem atrophy in PSP.(Josephs *et al*., 2008) Comparison of atrophic patterns between different pathologic FTLD groups is more challenging, as most studies had consecutive or convenient case combinations of FTLD-TDP and FTLD-Tau cases which can be biased towards local clinical expertise or patient subgroups with higher autopsy rates. Findings from these studies also reflected more the most prevalent clinical syndrome within each

pathologic group, and may be difficult to be generalized to a structural signature for a given FTLD pathology.

A few studies have focused on different atrophic patterns among patients with similar clinical syndromes along pathologic diagnoses. Compared to patients with pathologic AD, autopsy-confirmed cases of FTLD had more atrophy in frontal lobar regions, anterior cingulate gyri, and the insula.(Rabinovici *et al*., 2007) When cases of FTLD-TDP and FTLD-Tau – both clinically characterized by prominent behavior symptoms – were directly compared in two separate studies, no significant pattern of atrophy was sufficient to differentiate between the two pathologic groups.(Kim *et al*., 2007; Whitwell *et al*., 2004) However, when each specific pathologic diagnosis was examined individually, certain patterns were identified: atrophy in the bilateral orbitofrontal cortices, posterior superior temporal lobes, and posterior fusiform gyri in FTLD-TDP; bilateral dorsolateral prefrontal atrophy in Pick's disease with Pick bodies; right temporal and orbitofrontal atrophy in FTDP-17; frontoparietal cortical regions and subcortical nuclei in CBD; and brainstem, cortical, and adjacent white matter atrophy in PSP.(Whitwell *et al*., 2007; Whitwell *et al*., 2005) Whether these findings can be replicated in independent series and whether the group-level difference can be translated into diagnostic biomarkers at the individual level remain to be determined, although such analyses within, instead of across, clinical syndromes can circumvent certain false discoveries associated with syndromic diagnoses. For example, when patients with non-fluent PPA were examined according to autopsy- or CSF AD biomarker information, patients with AD had more posterior atrophy along the peri-sylvian region and patients with FTLD had more anterior atrophy.(Hu *et al*., 2010e) Similarly, when patients with CBS were examined according to autopsy information, patients with CBS due to CBD and AD both had atrophy in the basal ganglia, but patients with CBS due to AD had more temporal and inferior parietal atrophy.(Josephs *et al*., 2010a) Within certain clinical syndromes, patterns and severity of atrophy can differentiate between different FTLD pathologic types. Alternatively, comparisons can be made between clinical syndromes sharing the same pattern of dominant lobar atrophy. In one study including 20 patients with right temporal variant of FTD, all 8 patients with bv-FTD had FTLD-Tau, and all 12 patients with SD had FTLD-TDP.(Josephs *et al*., 2009) This strategy is intriguing since other potential areas of focal atrophy can be preferentially associated with certain clinical syndromes, including left temporal atrophy for SD and bv-FTD, left parietal atrophy for PPA and CBS, and right parietal atrophy for CBS and PCA. Future studies will be necessary for further understanding of such atrophy-syndrome pairing.

Significant progress has been made in other imaging modalities, including functional imaging such as positron emission tomography (PET) using $^{18}$F fluorodeoxyglucose (FDG), (Foster *et al*., 2007; Ishii *et al*., 1998) single-photon emission computed tomography (SPECT),(McMurtray *et al*., 2006; McNeill *et al*., 2007) diffusion tensor imaging (DTI), (Asmuth *et al*., 2008; Borroni *et al*., 2007; Whitwell *et al*., 2010; Zhang *et al*., 2009) and arterial spin labeling (ASL)(Alsop *et al*., 2000; Hu *et al*., 2010f) in the differential diagnosis of FTLD. Most of these studies have compared patients with FTLD against patients with AD, and the advancement in AD CSF biomarkers has allowed for more ante-mortem studies using the most modern imaging techniques. According to CSF AD biomarker profiles (Aβ42, tau, p-tau$_{181}$) consistent with AD or suggestive of a non-AD disorder, investigators can now derive group-level differences between pathologic cases of AD or non-AD disorders with similar clinical syndromes. This has been used in deriving an imaging signature of FTLD in ASL (frontal hypoperfusion with parietal hyperperfusion),(Hu *et al*., 2010f) and DTI studies are underway.(Hu *et al*., 2010g) Similar strategies are underway to identify functional or structural imaging signatures of FTLD-TDP or FTLD-Tau. In the meantime, the most promising use of structural imaging biomarkers (and possibly functional imaging biomarker) may be in disease staging, especially if biochemical biomarkers of

FTLD demonstrate a threshold-type phenomenon similar to CSF levels of Aβ42 in MCI and AD. Using boundary shift analysis, a study using serial structural imaging in autopsy-confirmed cases of FTLD showed different rates of atrophy over time among the different FTLD pathologic subyptes, with CBD and FTLD-TDP cases having the greatest longitudinal change, and PSP and DLB having the least.(Whitwell *et al*., 2007) While the rate of change may be influenced by pathology, the region of longitudinal atrophy may also be influenced by the clinical syndrome. For example, frontal insular network may be affected early in bv-FTD, while neorcortical atrophy can be found in mild disease and regions more associated with AD (parietal cortex, hippocampus) are affected late in the course.(Seeley *et al*., 2008) A similar technique showed correlation between MRI rates of atrophy and common clinical measures including scores on Mini-Mental Status Examination, Clinical Dementia Rating, and Frontal Assessment Battery in 32 clinically defined FTD patients.(Gordon *et al*., 2010) Taking advantage of the within-individual rate of volume change (even when insufficiently sensitive or specific to syndrome or pathology), serial measurements of brain volume can be a potential biomarker of response in therapeutic trials once patients are categorized according to clinical syndrome, most dominant region of atrophy, biochemical biomarkers, or a combination of these factors.(Knopman *et al*., 2009; Knopman *et al*., 2008) This approach is similar to the observations by ADNI investigators, (Jack *et al*., 2010) where CSF-based Aβ biomarkers become abnormal first to possibly identify subjects most at risk for future development of AD, followed by changes in neurodegenerative biomarkers (e.g. CSF total tau and p-tau$_{181}$, atrophy on MRI) and clinical symptoms that are better suited to follow the progression of disease.

No survey of FTLD imaging biomarkers would be complete without discussion on two recent technological advances: substrate-specific imaging and network based imaging. Substrate-specific imaging has generated much enthusiasm in biomarker research given its non-invasive nature and the ability to topographically characterize pathologic deposition. Most of the recent success in substrate-specific imaging related to neurodegenerative disorders has come from studies using ligands that bind to extracellular amyloid deposits in AD, including $^{11}$C-Pittsburgh Compound B ($^{11}$C-PIB)(Mormino *et al*., 2009; Wang *et al*., 2002) and $^{18}$F-AV-45 (florbetapir).(Choi *et al*., 2009; Wong *et al*., 2010) While their use in the differential diagnosis of AD and mild cognitive impairment is discussed elsewhere in this issue, amyloid imaging has been increasingly used in the differential diagnosis of FTLD, sometimes in lieu of CSF biomarkers. In one series of clinically characterized AD and FTD syndromes, $^{11}$C-PIB imaging revealed presence of amyloid deposition in 7 out of 7 AD cases and 4 out of 12 clinical FTD cases.(Rabinovici *et al*., 2007) While there was no autopsy information available on these patients, diagnostic prediction using FDG-PET scan provided complementary information. Importantly, in 3 out of 4 patients (2 bv-FTD, 2 SD) in whom diagnostic outcomes (AD or FTLD) differed between metabolic and amyloid imaging, $^{18}$F-FDG showed patterns consistent with FTLD despite the presence of amyloid deposition by $^{11}$C-PIB. When such studies were performed in clinical series of PPA(Rabinovici *et al*., 2008) and CBS(Lee *et al*., 2010) using amyloid imaging, results were found to mirror those reported in autopsy- or CSF AD biomarker-based studies.(Gross *et al*., 2010; Hu *et al*., 2010e; Josephs *et al*., 2010a; Mesulam *et al*., 2008) While direct comparison of CSF AD biomarkers and amyloid imaging compounds is not yet available, the use of “amyloid presence” as an exclusion criterion for FTLD pathology will invariably generate a suboptimal sensitivity in detecting all patients with FTLD pathology. This can be a particular concern as patients with autopsy-confirmed cases of FTLD (such as those reported in our autopsy-based multiplex biomarker studies(Hu *et al*., 2010b)) can have minor AD co-pathology reflected through positive AD biomarkers (CSF or imaging), and patients with genetic cases of FTLD (such as those with *PGRN* mutations(Mukherjee *et al*., 2006)) plus AD co-pathology can be misidentified as having AD. Therefore, the need for an imaging biomarker with positive predictive value for FTLD beyond the absence of amyloid

deposition is as important in imaging-based differential diagnosis of neurodegenerative disorders as it is in CSF- or plasma-based diagnostic algorithms. As FTLD disorders lack a clear extracellular target for ligand binding, receptor binding according to misregulated membrane-bound receptors (such as sortilin)(Hu *et al*., 2010a) or recruited cellular population may prove to be more useful than TDP-43 or tau binding ligands.

Finally, network based imaging analysis – examining correlated structural or functional changes across topographically distant brain regions – provided a new dimension of FTLD biomarker investigation. As multiple previous syndrome-based imaging have shown, each classic FTLD-related phenotype seems to be correlated with a network of atrophic brain regions (Table 3). When a region-of-interest approach was used to examine these connected regions in healthy control subjects, a strong network-specific correlation was found in terms of resting functional MRI activation pattern and volume variance.(Seeley *et al*., 2009) This finding supports the hypothesis that some of the seeming unrelated clinical symptoms (for example, language disorder and alien limb phenomenon in CBS) can be due to a network-level vulnerability that impairs distant rather than adjacent brain regions after disease onset. The proximity of some adjacent nodes belonging to very distinct networks can also potentially account for the various pathologic substrates for similar clinical FTLD syndromes (such as AD and FTLD both causing non-fluent PPA(Hu *et al*., 2010e)). An examination of the network-level imaging biomarker in future FTLD work can be fruitful in predicting underlying pathologic FTLD or FTLD subtypes, in addition to more conventional strategies such as single region structural or substrate-specific imaging approaches.(Zhou *et al*., 2010a)

## 5. Future challenges

As we reviewed here, significant progress has been made in the understanding of clinical, genetic, biochemical, pathologic, and radiologic characterization of FTLD related disorders despite the significant clinical heterogeneity and pathologic overlap. While studies on FTLD often lump patients into hypothesis-driven or convenient categories for the sake of power or simplicity, most FTLD investigators now share a certain degree of comfort in maneuvering through the maze of syndromic-pathologic admixture. Work centered around clinical syndromes (with or without pathologic correlation) has yielded useful information on brain-behavioral relationship and symptomatic progression of FTLD.(Gorno-Tempini *et al*., 2004; Grossman, 2010; Josephs, 2008; McKhann *et al*., 2001; Mesulam, 1982; Neary *et al*., 1998; Pick, 1892; Rascovsky *et al*., 2007a) Some of the biochemical studies suffer from small sample size and bias, although rigorous validation studies are underway. With progress in biomarker development for disorders such as AD in ADNI serving as a blueprint for FTLD biomarker studies (Table 4), the expanded use of ante-mortem biomarkers will likely herald the next chapter of FTLD investigation to allow for early detection of pathologic FTLD substrate. Reliable biomarkers may accurately identify prodromal subjects with familial FTLD with or without known mutations, and allow for better and timely recruitment of patients with known pathologic FTLD substrates for natural history studies, therapeutic trials, and other associated lines of investigation. Parallel to emerging technology for biomarker detection (analyte levels in biofluids, gray matter volume, white matter integrity, large scale network connectivity), novel analytical strategies on single time point classification and multiple time point correlation will also be necessary to elucidate meaningful biological relationships that would otherwise escape conventional statistical approaches. This may be especially relevant if there is discordance among biomarkers, (Rabinovici *et al*., 2007; Zhou *et al*., 2010a) and such discordance may need to be reconciled by yet more sophisticated algorithms beyond simple linear combinations. It may be only fitting that a network approach – be it biochemical analytes(Hu *et al*., 2010c; Hu *et al*., 2010d) or brain structures(Zhou *et al*., 2010a) – through collaboration with specialists in

complex applied mathematics and statistics would be the most suitable strategy to decode a family of disorders that defy the one syndrome-one pathology rule. If successful, these bodies of work can then be further developed beyond the first level TDP vs. Tau comparison. These can include biomarker discovery for those with FTLD subtypes (e.g., Type 1 pathology for FTLD-TDP, CBD instead of FTLD-Tau), tau and TDP-43-negative FTLDs such as FLTD with FUS,(Urwin *et al*., 2010) and FTLD of the same pathologic subtype but different prognosis.(Hu *et al*., 2009b)

An even greater barrier to progress of FTLD biology may be the separation of patients with the same disease in different subspecialty clinics (such as FTD-PSP patients in Cognitive Neurology or Movement Disorders clinics) based entirely on convention or reimbursement. As it is well recognized that FTLD continues to be a relatively uncommon disorder even when including those with ALS and PSP/CBS patients without dementia, the success of having a critical mass of FTLD patients at any level depends heavily on breaking down traditional administrative barriers that separate patients with dementia from those with other forms of neurodegenerative disorders. Similar to the depth associated with the creation of a comprehensive Alzheimer's disease center to involve radiologists, neuropsychologists, basic scientists, and clinical pharmacists among others,(Trojanowski *et al*., 2010a) the breadth of a comprehensive neurodegenerative research center must involve the talent and effort from Cognitive/Behavioral Neurology, Movement Disorders, and ALS/MND sections. As there is significant clinical, biochemical, pathologic, and radiologic overlap between cognitive-predominant forms of FTLD and the other disorders, future therapeutic strategies based on common pathologic substrates (TDP-43, tau, FUS) or susceptible regions (frontal-subcortical network, basal ganglia, motor neurons) will likely benefit more from cross pollination than continued separation. Effort to extend single center findings to a multi-center stage (demonstrated by ADNI) is also crucial beyond discovery and validation, as each stage of such multi-center studies promotes the harmonization of local approaches to the clinical, biochemical, pathologic, and radiologic characterization of FTLD.

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## Abbreviation List

| | |
|---|---|
| **AD** | Alzheimer's disease |
| **ALS/MND** | Amyotrophic lateral sclerosis/motor neuron disease |
| **ASL** | Arterial spin labeling |
| **CBS** | Corticobasal syndrome |
| **CBD** | Corticobasal degeneration |
| **CSF** | Cerebrospinal fluid |
| **DLB** | Dementia with Lewy bodies |
| **DTI** | Diffusion tensor imaging |

| | |
|---|---|
| **FTDP-17** | Frontotemporal dementia with parkinsonism linked to chromosome 17 |
| **FTLD** | Frontotemporal lobar degeneration |
| **FTLD-Tau** | Frontotemporal lobar degeneration with tau-immunoreactive lesions |
| **FTLD-TDP** | Frontotemporal lobar degeneration with TDP-immunoreactive lesions |
| **FUS** | fused-in-sarcoma |
| **MRI** | Magnetic resonance imaging |
| **PD** | Parkinson's disease |
| **PNFA** | Progressive non-fluent aphasia |
| **PPA** | Primary progressive aphasia |
| **PSP** | Progressive supranuclear palsy |
| **SD/SV-PPA** | Semantic dementia/semantic variant of primary progressive aphasia |

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## Table 1

Clinical syndromes associated with FTLD; pathologic causes shown in decreasing prevalence within each clinical syndrome.

| Syndromic Category | Subtypes | Pathologic association |
|---|---|---|
| Behavioral-variant frontotemporal dementia (bv-FTD) | bv-FTD | TDP-43, tau, AD, FUS, DLB |
| | FTD-ALS/FTD-MND | TDP-43, FUS, rarely tau |
| | FTD-PSP | Tau |
| Primary Progressive Aphasia (PPA)/ language variant of frontotemporal dementia | Semantic dementia/semantic variant PPA | TDP-43, AD, tau |
| | Logopenic progressive aphasia/logopenic variant of PPA | AD, TDP-43, tau |
| | Progressive non-fluent aphasia/non-fluent, agrammatic variant of PPA | Tau, TDP-43, AD, DLB |
| | PPA not otherwise specificed | AD |
| | Apraxia of speech | Tau |
| | PPA with ALS | TDP-43 |
| | PPA with CBS/PSP | Tau |
| Corticobasal syndrome (CBS)/ Corticobasal degeneration syndrome | CBS, motor predominant | Tau, AD, TDP-43, DLB |
| | CBS, cognitive predominant | |
| Progressive supranuclear palsy (PSP) | Richardson's syndrome | Tau, MSA |
| | PSP-Parkinsonism | |
| | PSP-Pure akinesia with gait freezing/primary progressive freezing gait | |
| Amyotrophic lateral sclerosis (ALS)/Motor neuron disease (MND) | Amyotrophic lateral sclerosis | TDP-43, FUS |
| | Primary lateral sclerosis | |
| | Upper motor neuron dominant motor neuron disease | |
| | Spinal muscular atrophy | |

**Table 2**

Potential biochemical biomarkers for FTLD or FTLD subtypes. See text for specific references.

| | Protein/Peptide | Disease Association |
|---|---|---|
| **Pathogenic proteins/peptides** | TDP-43 | Clinical FTD, ALS |
| | Progranulin | *PGRN* mutation cases |
| | Tau | Clinical FTD, FTLD-Tau |
| | Tau isoform ratio | Clinical PSP |
| **Structural proteins** | S100b | FTLD |
| | Neurofilament (light and heavy chain) | Clinical FTD, clinical PSP, ALS |
| **Neuropeptides** | granin-like neuroendocrine precursor | Clinical FTD |
| | pigment epithelium derived growth factor | Clinical FTD |
| | Angiopoietin-2 | FTLD-TDP, ALS |
| | Chromogranin B | Clinical FTD, ALS |
| | Cystatin C | Clinical FTD |
| | Agouti-related peptide | FTLD-TDP |
| | Adrenocorticotropic hormone | FTLD-TDP |
| | Orexin | Clinical PSP, CBS |
| **Inflammatory proteins** | IL-17 | FTLD-TDP |
| | IL-23 | FTLD-Tau |
| | Macrophage derived chemokine | FTLD-TDP |
| | Monocyte chemoattractant protein-1 | FTLD-TDP, ALS |
| | FAS | FTLD-TDP |
| | TRAIL-R3 | FTLD-TDP |
| | Complement protein C4d | Clinical PSP, ALS |
| **Apolipoproteins** | ApoB | FTLD |
| | ApoE | Clinical FTD |
| **Other** | Retinol-binding protein | Clinical FTD |

## Table 3

Regions of brain atrophy associated with FTLD and behavioral alteration(s) correlated with each region. See text for specific references.

| Clinical Syndrome | Regions of Atrophy | Behavioral correlation |
|---|---|---|
| Behavioral variant frontotemporal dementia | Dorsolateral prefrontal cortex, right | Apathy |
| | Anterior cingulate cortex | |
| | Insula | Binge eating (right) |
| | Orbitofrontal cortex | Disinhibition; poor emotional comprehension; disagreeableness |
| | Left motor cortex | |
| | Posterolateral temporal cortex, right | |
| | Amygdala, right | Poor emotional comprehension |
| Semantic dementia | Anterior inferior temporal gyrus, left | Poor sentence comprehension |
| | Anterior superior temporal gyrus, left | Loss of single word meaning |
| | Right temporal lobe | Poor comprehension of emotion, prosopagnosia |
| | Posterior amygdale | |
| | Visual association cortex | Degraded visual-perceptual feature knowledge of concrete object and actions |
| | Ventromedial frontal cortex | |
| | White matter | |
| Progressive non-fluent aphasia | Inferior frontal gyrus, left | Poor fluency (words per minute), agrammatism |
| | Precentral gyrus, left | |
| | Superior premotor cortex | Apraxia of speech, poor fluency |
| | Middle frontal gyrus | |
| | Caudate nuclei | |
| | Putamen, left | |
| Corticobasal syndrome | Premotor cortex | Apraxia, apraxia of speech (left) |
| | Subcortical white matter, frontal lobe | Parkinsonism |
| | Posterior temporal lobe | Neuropsychiatric symptoms |
| | Parietal lobe | Inability to correct praxis errors, calculation difficulties |
| | Basal ganglia | |
| | Corpus callosum | Possible alien limb phenomenon |

**Table 4**

Multi-modal biomarker combinations for AD and FTLD.

| | AD | FTLD | Potential clinical utility |
|---|---|---|---|
| Clinical characterization of dominant syndrome | Differentiation between:<br>-dementia of the Alzheimer's type<br>- focal AD syndromes (such as posterior cortical atrophy)<br>-mild cognitive impairment | Differentiation between:<br>-bv-FTD<br>-PPA (SD, PNFA, LPA)<br>-CBS/PSP<br>-FTD/PPA with ALS | Initial classification<br>Prognosis<br>Symptom-based treatment |
| Neuropsychological analysis | -Impaired recall<br>-Impairment in focal syndromes reflects affected brain region(s) | -Impairments reflect syndromes<br>-Relative performances in paired subtests may reflect pathology | Staging<br>Tracking of progression<br>Monitoring of treatment response<br>Possible pathologic prediction |
| Genetic analysis | Pathogenic mutations: APP, PS1, PS2<br>Risk gene: APOE | Pathogenic mutations: MAPT, PGRN, TDPBP, FUS, CHMP2B, VCP<br>Risk genes: MAPT, TMEM 106B | Pathologic prediction<br>Mutation-based treatment<br>Risk stratification |
| Biofluid analysis | CSF: Aβ42, tau, p-tau$_{181}$ levels<br>Plasma & serum: multiplex panels | CSF: tau, TDP-43, multiplex panel<br>Plasma & serum: TDP-43, progranulin | Pathologic prediction<br>Staging<br>Monitoring of treatment response |
| Imaging | MRI: hippocampal & parietal atrophy<br>PET: temporal-parietal hypometabolism<br>Amyloid imaging: positive<br>DTI: temporal & parietal dysfunction, mild<br>ASL: frontal hyperprefusion, parietal hypoperfusion | MRI: atrophy reflects syndrome<br>PET: hypometabolism reflects syndrome<br>Amyloid imaging: mostly negative,<br>but can be positive<br>DTI: frontal & temporal dysfunction, more severe<br>ASL: frontal hypoperfusion, parietal hyperperfusion | Disease confirmation<br>Staging<br>Tracking of progression<br>Monitoring of treatment response |