Published in final edited form as:

J Mol Neurosci. 2011 November ; 45(3): 366–371. doi:10.1007/s12031-011-9597-0.

BIOMARKERS TO IDENTIFY THE PATHOLOGICAL BASIS FOR FRONTOTEMPORAL LOBAR DEGENERATION

Murray Grossman

Department of Neurology, Perelman School of Medicine, University of Pennsylvania

Abstract

Recent findings assessing the utility of biomarkers are reviewed that help identify the basis for disease in patients with frontotemporal lobar degeneration (FTLD) spectrum pathology. Biofluid studies identify about 15% of patients with FTLD due to a genetic mutation that is associated with the specific histopathologic features of TDP-43 or a tauopathy. Other genetically-based risk factors and targeted proteomic searches of plasma and cerebrospinal fluid have suggested additional markers that may be useful in sporadic cases of FTLD. While progress has been made in developing biomarkers for FTLD, additional work is needed to extend these advances so that the histopathologic abnormality causing FTLD can be specified in an individual patient.

Keywords

frontotemporal lobar degeneration; biomarker; cerebrospinal fluid; neuroimaging

Treatment trials for frontotemporal lobar degeneration (FTLD) are beginning to emerge. These trials are targeted at the histopathologic abnormality causing FTLD. The goal of these trials is to change the natural history of this disorder. Detailed descriptions have been developed that characterize the spectrum of FTLD pathology(1). One common abnormality is FTLD-TDP. This is due to the accumulation of ubiquitinated and hyperphosphorylated trans-active DNA-binding protein of ~43 kD (TDP-43)(2). A second family of conditions associated with the accumulation of the microtubule-associated protein tau constitutes another common cause of FTLD – although somewhat diverse biochemically, these pathologies are collectively known as FTLD-tau(3). Conditions contributing to the family of tauopathies include dementia with Pick bodies, corticobasal degeneration and progressive supranuclear palsy. A less common histopathologic finding is FTLD-FUS, related to fused-in-sarcoma immunoreactive inclusions(4).

CLINICAL AND IMAGING MARKERS OF DISEASE

Clinical assessment plays an important screening role in the initial identification of patients with a phenotype corresponding to this FTLD spectrum of pathology. This is reasonable because there is some agreement between a clinical FTLD syndrome and an underlying pathological abnormality. Patients with semantic dementia, also known as the semantic variant of primary progressive aphasia (svPPA), often have TDP-43 pathology(5). Patients with progressive non-fluent aphasia, also known as the non-fluent/agrammatic variant of PPA (naPPA), frequently have a tauopathy(6). Other PPA patients have an atypical, aphasic form of Alzheimer's disease (AD), also known as the logopenic variant of PPA (lvPPA),

Please address correspondence to: Murray Grossman, Department of Neurology – 2 Gibson, University of Pennsylvania School of Medicine, 3400 Spruce St, Philadelphia, PA 19104-4283, Voice: 215-662-3361; fax: 215-349-8464; mgrossma@mail.med.upenn.edu.

and this may overlap with PPA due to FTLN spectrum pathology(7). A recent survey of unselected clinical-pathological series of PPA patients confirmed this general picture, but emphasized that the association of a clinical phenotype with histopathology at autopsy is less reliable in individual patients(8). The situation is more confusing for behavioral-variant FTD (bvFTD), where rare studies attempt to distinguish the clinical characteristics of a social disorder related to FTLN-tau or FTLN-TDP(9). These patients may be indistinguishable from cases with a so-called frontal variant of autopsy-proven AD (fvAD) (10).

Quantitative neuropsychological measures of language and cognition in autopsy-proven cases of FTLN provide another approach to identifying the histopathology underlying patients in this clinical spectrum of disease. Patients with a TDP-43 proteinopathy are significantly more impaired than patients with a tauopathy or AD pathology on measures of confrontation naming and category naming fluency guided by the letters F, A, and S(11–13). By comparison, patients with tau-positive pathology are significantly more impaired than patients with a TDP-43 proteinopathy and patients with AD pathology on non-linguistic measures of executive functioning involving visual constructions and reverse digit span(12, 13). Within the PPA spectrum, episodic memory is relatively impaired in lvPPA patients with AD pathology compared to PPA patients with FTLN-tau or FTLN-TDP pathology(3, 14). Despite the value of this approach at a group level, follow-up observations have shown that quantitative neuropsychological measures are unreliable at identifying histopathology in individual patients(15).

Structural and functional imaging studies associate the distinct features of a clinical FTLN syndrome with partially selective interruptions of large-scale networks that are associated with PPA or bvFTD. These anatomic distributions of disease also may reflect a particular histopathologic abnormality.

An example of the anatomic distribution of cortical thinning in the three major PPA syndromes is illustrated in Figure 1(8). naPPA is related largely to anterior peri-Sylvian atrophy involving inferior, opercular, insular and dorsolateral portions of the left frontal lobe(16, 17). Longitudinal imaging studies are rare, but personal observations suggest that atrophy associated with PNFA often extends medially into orbital frontal and anterior cingulate regions, inferiorly into the anterior superior temporal lobe, and posteriorly along the Sylvian fissure into the parietal lobe. svPPA has a different anatomic distribution, causing left anterior temporal atrophy that affects lateral and ventral surfaces as well as the anterior hippocampus and the amygdala(18, 19). Longitudinal studies show atrophy extending in a posterior and superior direction in the ipsilateral temporal lobe, and often involve the adjacent frontal lobe and anterior temporal regions of the right hemisphere(20–22). lvPPA is associated with left posterior-peri-Sylvian atrophy in the area of temporal-parietal junction(16). Longitudinal imaging tends to extend into more inferior regions of the temporal lobe, and anteriorly along the Sylvian fissure into the frontal lobe.

Comparative imaging studies in patients with pathologically-confirmed disease are crucial for validating an association between an anatomic distribution of disease and an underlying histopathologic abnormality. However, these studies have been rare. MRI gray matter thinning has been assessed in small groups of naPPA patients with tau-positive disease and svPPA patients with FTLN-U pathology presumably due to TDP-43(23). The naPPA patients showed superior temporal and inferior frontal thinning that was more prominent in the left hemisphere than the right hemisphere, and the svPPA patients showed prominent left anterior temporal thinning.

Another study assessed the validity of MRI structural imaging in 34 non-fluent PPA patients with autopsy- or CSF-based evidence consistent with underlying FTLD or AD pathology(15). Statistically significant differences in the anatomic distribution of cortical atrophy were described in the FTLD and AD subgroups, but a receiver operating characteristic (ROC) curve analysis of cortical atrophy revealed an area under the curve of only 0.64, with 72.7% sensitivity and 66.7% specificity.

Recent work also has demonstrated the utility of diffusion tensor imaging (DTI) to distinguish clinical syndromes on the basis of white matter abnormalities, although DTI studies in patients with autopsy-confirmed disease are rare. One preliminary report evaluated clinically-diagnosed FTLD patients who had autopsy- or CSF- based biomarkers consistent with FTLD or AD pathology(24). Significantly reduced fractional anisotropy (FA) was seen in FTLD compared to AD in the anterior corpus callosum and anterior portions of the inferior longitudinal fasciculus.

Another study combined cortical atrophy and FA changes to classify 50 individual cases of clinically diagnosed FTLD who had autopsy- or CSF-based findings consistent with FTLD or AD pathology(25). A support vector machine technique selected the optimal voxels from T1 and DTI imaging, and applied the resulting algorithm to categorize individual participants. In FTLD, changes were most prominent in frontal and anterior temporal regions, while changes in temporal-parietal brain areas were more evident in AD. The algorithm combining T1 and DTI accurately categorized 49 (98%) of the 50 participants.

Arterial spin labeling (ASL) perfusion MRI is a functional neuroimaging technique that has the potential to be more sensitive than structural MRI imaging because differences do not depend on a late change that involves death in a large population of neurons. Using ASL, abnormal hypoperfusion in frontal regions and hyperperfusion in parietal regions was seen in patients with autopsy- and CSF- defined FTLD(26). Moreover, in contrast to patients with autopsy- and CSF-defined AD, perfusion in FTLD was significantly lower in frontal regions and significantly elevated in temporal-parietal regions.

PET and SPECT functional imaging technologies incorporate tracers such as Pittsburgh Compound B (PiB) that radiolabel beta-amyloid (A)(27). This protein accumulates in AD but not FTLD, and thus may help distinguish between cases of PPA or a social disorder that may be caused by AD rather than FTLD spectrum pathology. One report described reduced PiB uptake in eight of 12 clinically diagnosed FTLD patients(28). A follow-up study noted PiB uptake in all four of the lvPPA patients who were evaluated, and signal was strongest in a left temporal-parietal distribution(29). By comparison, PiB uptake was less common in other PPA syndromes, where left frontal uptake was seen in only one of six naPPA patients and left temporal uptake was seen in only one of five svPPA patients. Unfortunately there was no autopsy confirmation of disease in the handful of patients that have been studied.

BIOFLUID MARKERS OF DISEASE

While clinical phenotype, quantitative neuropsychology and brain imaging provide useful screening information suggesting FTLD spectrum pathology, additional information is needed to define the histopathologic abnormality in an individual patient with PPA or bvFTD. Biomarkers thus must be developed to supplement the clinical examination. A biomarker is a validated measure that reliably reflects the underlying pathology of a disease. This is crucial in FTLD, where a clinical phenotype can be associated with several different pathologies. Some biomarkers are categorical and provide diagnostic information. This class of biomarkers must distinguish between healthy controls and patients. A panel of biomarkers may be needed to identify each of several neurodegenerative diseases. This would confer specificity to support distinguishing between different age-associated neurodegenerative

conditions like FTLN-TDP, FTLN-tau and AD. Other biomarkers may reflect disease severity and the course of the condition. This class of biomarkers would be useful in treatment trials to determine whether the disease is responding to the treatment. Several biomarker modalities are potentially available to help determine the basis for FTLN, including blood and serum studies, and studies of analytes in the cerebrospinal fluid (CSF).

Familial disorders are frequent in FTLN. Thus, one important source of information about the pathology causing a FTLN syndrome is DNA found in blood samples. Up to 45% of index cases can have a strongly positive family history(30, 31), and about 15% of FTLN patients have an identifiable mutation. , naPPA and bvFTD may be associated with a mutation of the *GRN* gene coding progranulin (*PGRN*) on chromosome 17(32, 33). *GRN* mutations are reliably associated with FTLN-TDP pathology(34–37). Less common mutations associated with FTLN-TDP pathology include VCP on chromosome 9, CHMP2B on chromosome 3, and TARDBP on chromosome 1. Other familial patients with an FTLN syndrome have a mutation of the microtubule-associated protein tau (*MAPT*) gene coding tau on chromosome 17. This is associated with tau histopathology(38–40). An important point of caution is that a clinical FTLN syndrome can be highly variable in patients with the identical *GRN* mutation(41) or members of a family with the same mutation of *GRN*(42, 43). Likewise, the phenotype associated with a specific *MAPT* mutation may be highly variable(44).

These genetic factors may be used to help define the risk associated with the pathologic basis for FTLN in sporadic cases. Tau haplotypes are derived from the region of chromosome 17 where the *MAPT* gene is coded. The H1 haplotype is over-represented in conditions associated with tau pathology such as corticobasal degeneration, progressive supranuclear palsy, and sporadic FTLN(45–47). However, a tau haplotype has been associated directly with tau pathology only rarely(48). A recent genome-wide association study (GWAS) of over 1,000 patients with autopsy-confirmed CBD and PSP has identified several highly significant single nucleotide polymorphisms (SNPs) that are risk factors for FTLN-tau. Some are associated with the *MAPT* region coding tau at 17q21, including rs8070723 and rs242557(49). Other highly significant SNPs include rs1411478 at chromosome 1q25.3 coding for STX6, rs1768208 coding for MOBP at chromosome 3p22.1, and rs7299371 coding for NELL2 at chromosome 12q12. Each of these SNPs is associated with the biology of these tauopathies: For example, MOBP appears to be strongly associated with brainstem white matter pathology in PSP.

Similar work has been pursued in identifying markers of TDP-43 pathology. Homozygosity for the T allele at rs5848 in the region coding *GRN* on chromosome 17 appears to be an important risk marker for FTLN-TDP pathology(50). A risk biomarker associated with TDP-43 pathology was derived from a GWAS of >500 autopsy-proven cases with FTLN-TDP pathology. An increased risk for the presence of TDP-43 pathology was associated with TMEM106B, coded on chromosome 7p21. The proportions of FTLN patients (46%) and AD patients (22%) with elevated plasma levels of TDP-43 correspond roughly to the percentages of these groups with TDP-43 detected in the brains at autopsy(51). Plasma levels of phosphorylated TDP-43 are correlated with the density of FTLN-TDP brain pathology, but plasma levels of TDP-43 do not distinguish between patients with FTLN and AD(52).

Cerebrospinal fluid (CSF) is another potential source of biomarker information. About 20% of individual patients with FTLN had significantly low levels of CSF tau relative to healthy controls, although this was never seen in patients with AD(53). In patients with known pathology, the tau:A β _{1–42} ratio was significantly lower in FTLN than AD. A ROC curve analysis showed that a ratio of 1.06 had excellent sensitivity and specificity for

distinguishing FTLT from AD(54), although this was based on an ELISA analysis of CSF that has considerably greater variability than recent measurement techniques involving a Luminex platform(55).

TDP-43 levels have been assayed in the CSF of patients with a clinical diagnosis of FTLT. Analyses also have been performed in ALS, where over 95% of patients with sporadic disease have TDP-43 pathology(56, 57). Significantly elevated CSF levels of TDP-43 have been found. However, the participants in these studies did not have autopsy-proven disease, and TDP-43 levels of patients overlapped with those of controls.

A targeted proteomic search has identified a panel of novel CSF biomarkers that distinguishes between autopsy-confirmed cases of AD and a group of non-AD patients where 92% had FTLT spectrum pathology(58). Phosphorylated-tau181, A β ₁₋₄₂, and agouti-related peptide (AgRP) were found to be useful classifying analytes. A follow-up study examined the CSF of autopsy-confirmed cases with FTLT-TDP and FTLT-tau pathology(59). In addition to AgRP, four analytes were identified as distinguishing biomarkers, including adrenocorticotrophic hormone (ACTH), eotaxin-3, Fas, and interleukin 17 (IL-17). Together, these analytes distinguished between FTLT-tau and FTLT-TDP with reasonable sensitivity and specificity.

Once screened by clinical and imaging markers of disease, recent advances suggest that biofluid biomarkers are likely to be useful in the identification of the specific histopathologic abnormality causing a FTLT clinical syndrome. A two-stage diagnostic approach thus may help identify the histopathology abnormality in FTLT. First, imaging studies appear to be useful at distinguishing FTLT from patients with AD pathology. Based on a family history, biomarkers in blood then can be obtained to identify patients with a genetic mutation that is associated with FTLT-tau or FTLT-TDP. Unfortunately, this represents only about 15% of patients with a FTLT clinical syndrome. Studies of CSF and plasma are becoming increasingly useful at identifying a specific histopathologic abnormality in the remaining patients with a sporadic FTLT syndrome. Although not yet definitive, these findings suggest that will be able to identify patients who are eligible for trials targeted a specific histopathologic abnormality causing FTLT.

Acknowledgments

This report was supported in part by funding from NIH (AG15116, AG17586, NS44266, NS53488, AG32953)

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FIGURE 1. CORTICAL ATROPHY CORRESPONDING TO PRIMARY PROGRESSIVE APHASIA SYNDROMES

NOTE: 1. Frontal = non-fluent/agrammatic variant PPA; anterior temporal = semantic variant; posterior temporal-parietal = logopenic variant.