Editorial

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Biomarkers in Medicine

Biomarkers in frontotemporal dementia

"Although there are currently no drugs that can delay the onset or prevent the progression of frontotemporal dementia ... recent molecular advances in frontotemporal dementia have suggested promising avenues for treatment."

Keywords: C9orf72 • frontotemporal dementia • FUS • progranulin • tau • TDP-43

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Frontotemporal dementia (FTD) is a clinically, genetically and pathologically heterogeneous neurodegenerative disorder that selectively affects the frontal and anterior temporal lobes of the brain. It is a common cause of young-onset dementia (i.e., dementia developing under the age of 65 years) with an estimated prevalence of 15–22/100,000 individuals [1]. FTD usually presents with behavioral disturbance (behavioral variant FTD) or language impairment (primary progressive aphasia), but there is also overlap with motor neurone disease and the atypical parkinsonian disorders, corticobasal syndrome and progressive supranuclear palsy [1]. At postmortem neuronal inclusions containing tau, TDP-43 or FUS protein are seen in the majority of cases. However, a poor correlation between clinical syndrome and underlying pathology means that it is difficult to diagnose the underlying molecular basis during life, except in approximately a third of cases which are familial, caused by mutations in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) or *C9orf72* [2]. Although there are currently no drugs that can delay the onset or prevent the progression of FTD, or even specific symptomatic therapies with clear benefit, recent molecular advances in FTD have suggested promising avenues for treatment. However, the heterogeneity of FTD means that stratification for clinical trials is challenging; in sporadic FTD the inability to diagnose the underlying molecular pathology in life currently makes disease-modifying therapy trials difficult. Furthermore, biomarkers of disease progression that can support the interpretation of clinical trials are also lacking.

MRI studies of FTD have mostly examined cross-sectional changes in gray matter atrophy using volumetric T1 MRI, aiming to identify specific patterns correlating with a particular clinical syndrome or genetic/pathological cause [3]. Previous work has shown that there are some relatively distinct patterns of atrophy in certain genetic and pathological groups, for example, symmetrical anterior medial temporal lobe atrophy in *MAPT* mutations and asymmetrical anterior/inferior temporal lobe atrophy in the type C subtype of FTLD–TDP [4–6]. However, it remains difficult to stratify the FTD spectrum adequately using only structural T1 imaging, and while there is preliminary work suggesting that using other MRI modalities may be helpful in stratification of FTD (e.g. diffusion tensor imaging may be useful in distinguishing FTD due to tau from that due to TDP-43 pathology [7]), their utility remains unclear. By contrast, there is some evidence that longitudinal imaging measures may be useful as biomarkers of disease progression: studies have shown that whole brain atrophy rates measured at 12-month intervals can produce feasible sample size estimates for trials in FTD [8,9], with more focal measures, such as lobar volumes, shown to produce smaller sample sizes [10]. However, little is currently known regarding the variability in rate and pattern of disease progression, as measured by change in longitudinal imaging markers.

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Cerebrospinal fluid (CSF) or serum measures have so far shown limited utility as biomarkers of disease onset or progression for disorders in the FTD spectrum. Serum progranulin concentration correlates with the presence of a pathogenic *GRN* mutation and has been shown to be equally abnormal in the premanifest phase before symptoms develop [11]. However, it does not seem to change over time, therefore, symptom onset or how the disease will change over time cannot be predicted.

> "Cerebrospinal fluid or serum measures have so far shown limited utility as biomarkers of disease onset or progression for disorders in the frontotemporal dementia spectrum."

Reliable measures of the underlying pathology in FTD have yet to be found. While a raised CSF tau/Aβ42 ratio can distinguish Alzheimer's disease (AD) from FTD pathologically [12], CSF tau does not seem to be a direct marker of tau pathology: levels are variable in FTD and may be normal [12], including in those with mutations in the *MAPT* gene [13]. TDP-43 has been measured in both plasma and CSF [14,15], and a recent study of phosphorylated TDP-43 in plasma found raised levels in patients with FTD carrying *C9orf72* or *GRN* mutations – that is, genetic forms of FTD known to be associated with TDP-43 pathology [15]. However, it has yet to be shown that plasma or CSF TDP-43 can reliably distinguish FTD due to TDP-43 pathology from cases due to tau or FUS pathology. A number of recent studies have therefore investigated whether other markers may distinguish these different pathological subtypes [16,17]. In one study, elevated CSF levels of neurofilament light chain were particularly seen in those with TDP-43 or FUS compared with tau pathology [16]. A larger study investigated a series of CSF markers and found that a panel of five proteins showed promise for distinguishing patients with TDP-43 from those with tau pathology [17]. However, in a further validation study, the most promising biomarker was reduced phosphotau-181/total tau ratio, which appeared to be a biomarker of TDP-43 pathology and could differentiate it from FTD due to tau pathology with a sensitivity of 82%, although, with a specificity of only 62% [18].

There are no studies investigating CSF or serum measures of disease progression in FTD, although, it has recently been suggested that CSF neurofilament light chain may be a marker of disease severity in FTD [19]. Further work will need to be carried out to confirm the utility of this and other markers in tracking FTD.

An area of particular interest in FTD biomarker discovery is that of neuroinflammation and microglial activation, with studies demonstrating the importance of these processes in the pathophysiology of FTD [20,21]. However, preliminary studies of inflammatory markers in FTD have been inconsistent: one study has shown raised serum IL-6 levels in patients with *GRN* mutations but normal TNF-α [22], whereas another study showed raised serum TNF-α in patients with *GRN* mutations and semantic dementia [23].

Another area of future interest will be molecular imaging of the underlying pathology in FTD. Until recently, no PET ligands have been available to investigate this, however, a recent study has shown that a novel ligand (T807) binds to tau in AD [24], although, it has yet to be shown whether it will be abnormal in patients with the different tau pathologies associated with FTD.

Studies of familial AD have provided evidence of a dynamic biomarker model reflecting molecular and functional changes during preclinical and clinical disease stages of AD. According to this model changes are seen up to 25 years presymptomatically in CSF markers (Aβ42) followed by molecular imaging (amyloid PET) abnormalities around 15 years prior to expected symptom onset and then changes in structural imaging markers, neuropsychometric measures (tests of episodic memory) and lastly the development of clinical symptoms and subsequent functional decline [25]. Such a model has not yet been examined in FTD. Studies of presymptomatic genetic FTD have been limited mostly to case reports and small-case series [26], although, there is limited evidence for premanifest structural imaging changes, with more recent studies showing changes in structural and functional connectivity even earlier [27,28]. Larger studies to investigate this further are now underway including the GENFI, a multicenter study across Europe and Canada of presymptomatic genetic FTD [26].

While progress has been made in recent years in understanding the molecular pathology of FTD, this has not yet translated into robust biomarkers of disease onset and progression that could have utility in clinical trials. However, with the development of candidate therapies for FTD likely to occur in the next few years, it is of great importance that the field is ready for such trials and adequate studies of biomarkers in large cohorts have been performed.

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References

1 Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. *J. Neurol. Neurosurg. Psychiatry* 82(5), 476–486 (2011).

2 Rohrer JD, Warren JD. Phenotypic signatures of genetic frontotemporal dementia. *Curr. Opin. Neurol.* 24(6), 542–549 (2011).

3 Rohrer JD, Rosen H. Neuroimaging of frontotemporal dementia. *Int. Rev. Psychiatry* 25(2), 221–229 (2013).

4 Rohrer JD, Ridgway GR, Modat M *et al.* Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by *progranulin* and *tau* mutations. *Neuroimage* 53(3), 1070–1076 (2010).

5 Rohrer JD, Lashley T, Schott JM *et al.* Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain* 134(9), 2565–2581 (2011).

6 Whitwell JL, Weigand SD, Boeve BF *et al.* Neuroimaging signatures of frontotemporal dementia genetics: *C9ORF72*, tau, progranulin and sporadics. *Brain* 135(Pt 3), 794–806 (2012).

7 McMillan CT, Irwin DJ, Avants BB *et al.* White matter imaging helps dissociate tau from TDP-43 in frontotemporal lobar degeneration. *J. Neurol. Neurosurg. Psychiatry* 84(9), 949–955 (2013).

8 Knopman DS, Kramer JH, Boeve BF *et al.* Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain* 131(Pt 11), 2957–2968 (2008).

9 Gordon E, Rohrer JD, Kim LG *et al.* Measuring disease progression in frontotemporal lobar degeneration: a clinical and MRI study. *Neurology* 74(8), 666–673 (2010).

10 Rohrer JD, Clarkson MJ, Kittus R *et al.* Rates of hemispheric and lobar atrophy in the language variants of frontotemporal lobar degeneration. *J. Alzheimers Dis.* 30(2), 407–411 (2012).

11 Ghidoni R, Stoppani E, Rossi G *et al.* Optimal plasma progranulin cutoff value for predicting null progranulin mutations in neurodegenerative diseases: a multicenter Italian study. *Neurodegener. Dis.* 9(3), 121–127 (2012).

12 Bian H, Van Swieten JC, Leight S *et al.* CSF biomarkers in frontotemporal lobar degeneration with known pathology. *Neurology* 70(19 Pt 2), 1827–1835 (2008).

13 Rosso SM, van Herpen E, Pijnenburg YA *et al.* Total tau and phosphorylated tau 181 levels in the cerebrospinal fluid of patients with frontotemporal dementia due to P301L and G272V *tau* mutations. *Arch Neurol.* 60(9), 1209–1213 (2003).

14 Foulds PG, Davidson Y, Mishra M. Plasma phosphorylated-TDP-43 protein levels correlate with brain pathology in frontotemporal lobar degeneration. *Acta Neuropathol.* 118(5), 647–658 (2009).

15 Suárez-Calvet M, Dols-Icardo O, Lladó A. Plasma phosphorylated TDP-43 levels are elevated in patients with frontotemporal dementia carrying a *C9orf72* repeat expansion or a *GRN* mutation. *J. Neurol. Neurosurg. Psychiatry* doi:10.1136/jnnp-2013–305972 (2013) (Epub ahead of print).

16 Landqvist Waldö M, Frizell Santillo A, Passant U *et al.* Cerebrospinal fluid neurofilament light chain protein levels in subtypes of frontotemporal dementia. *BMC Neurol.* 13, 54 (2013).

17 Hu WT, Chen-Plotkin A, Grossman M *et al.* Novel CSF biomarkers for frontotemporal lobar degenerations. *Neurology* 75(23), 2079–2086 (2010).

18 Hu WT, Watts K, Grossman M *et al.* Reduced CSF p-tau181 to tau ratio is a biomarker for FTLD–TDP. *Neurology* 81(22), 1945–1952 (2013).

19 Scherling CS, Hall T, Berisha F. Cerebrospinal fluid neurofilament concentration reflects disease severity in frontotemporal degeneration. *Ann Neurol.* doi:10.1002/ana.24052 (2013) (Epub ahead of print).

20 Martens LH, Zhang J, Barmada SJ *et al.* Progranulin deficiency promotes neuroinflammation and neuron loss following toxin-induced injury. *J. Clin. Invest.* 122(11), 3955–3959 (2012).

21 Lant SB, Robinson AC, Thompson JC. Patterns of microglial cell activation in frontotemporal lobar degeneration. *Neuropathol. Appl. Neurobiol.* doi:10.1111/nan.12092 (2013) (Epub ahead of print).

22 Bossù P, Salani F, Alberici A *et al.* Loss of function mutations in the *progranulin* gene are related to pro-inflammatory cytokine dysregulation in frontotemporal lobar degeneration patients. *J. Neuroinflammation* 8, 65 (2011).

23 Miller ZA, Rankin KP, Graff-Radford NR. TDP-43 frontotemporal lobar degeneration and autoimmune disease. *J. Neurol. Neurosurg. Psychiatry* 84(9), 956–962 (2013).

24 Chien DT, Bahri S, Szardenings AK *et al.* Early clinical PET imaging results with the novel PHF-tauradioligand [F-18]-T807. *J. Alzheimers Dis.* 34(2), 457–468 (2013).

25 Bateman RJ, Xiong C, Benzinger TL *et al.*; Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N. Engl. J. Med.* 367(9), 795–804 (2012).

26 Rohrer JD, Warren JD, Fox NC, Rossor MN. Presymptomatic studies in genetic frontotemporal dementia. *Rev. Neurol. (Paris)* 169(10), 820–824 (2013).

27 Borroni B, Alberici A, Cercignani M *et al.* Granulin mutation drives brain damage and reorganization from preclinical to symptomatic FTLD. *Neurobiol. Aging* 33(10), 2506–2520 (2012).

28 Dopper EG, Rombouts SA, Jiskoot LC *et al.* Structural and functional brain connectivity in presymptomatic familial frontotemporal dementia. *Neurology* 80(9), 814–823 (2013).