Proteomic analysis of TDP-43 pathology in Frontotemporal Dementia

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INTRODUCTION

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder presenting with behavioural or speech problems. Identification of the underlying molecular abnormality during life remains elusive, and there are no reliable biomarkers of TDP-43 proteinopathies. Proteomic analysis of the TDP-43 proteinopathies provides a unique opportunity to better understand the disease-associated pathways and determine surrogate biomarkers of TDP-43 pathology.

METHODS

We set out to investigate the proteomic profile of the TDP-43 proteinopathies using label-free quantitative mass spectrometry. 15 cases were selected: 9 had histologically confirmed TDP-43 inclusions as their primary pathology, 3 had Alzheimer's disease (AD) pathology (without TDP-43 disease) and 3 were healthy controls. Three regions from each case were examined: frontal lobe, temporal lobe and hippocampus. Samples were pooled according to pathological group and brain region. Samples were processed as outlined in figure 1 (below), before mass spectrometric analysis (Synapt G2-Si nanoAcquity LC system).

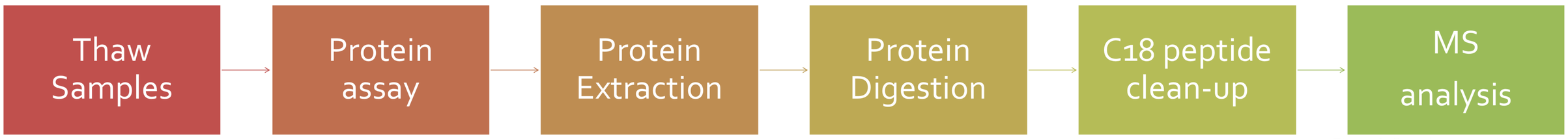


Figure 1: Sample preparation protocol

RESULTS

21 proteins were significantly upregulated in TDP-43 proteinopathies compared with AD and 30 proteins were downregulated. 37 proteins have previously been implicated in disease pathogenesis (highlighted in bold in tables 1 & 2) but 14 are novel.

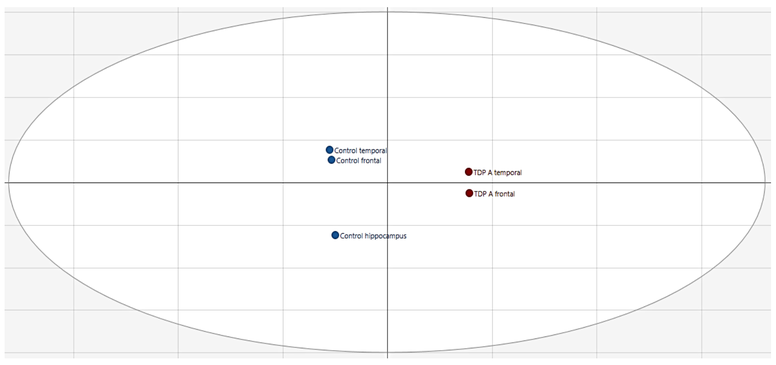
Of particular interest, comparisons with the existing literature has highlighted those candidates which may have the most potential: in Laferrière's proteomic study using extracted TDP-43, *TUBA4A (*Tubulin Alpha 4a), *PPP3R1 (*Protein Phosphatase 3 Regulatory Subunit B, Alpha) and *TXN* (Thioredoxin) levels were also altered with the former being upregulated and the latter two being downregulation in disease, mirroring my findings.

Upregulated			
Gene	Fold change	Gene	Fold change
RPS16	**38.4**	**STOM**	**2.1**
RPL15	**9.4**	**H3F3A**	**2.6**
QPRT	**8.4**	CCT6A	2.6
TUBA4A	**7.4**	TPD52L2	1.8
PGLS	**3.2**	ALDH6A1	2.3
GLUD1	**3.8**	PPA1	3.6
NDUFB6	**3.5**	**SFXN1**	**2.3**
BCAS1	**2.7**	ISOC2	2.1
CRYL1	3.3	**GNAQ**	**1.6**
MT-CO2	**4**	**GSTP1**	**2.5**
DPYSL4	**3.2**		

Downregulated			
Gene	Fold change	Gene	Fold change
HOMER1	**-2.0**	**FSCN1**	**-2.4**
CALM1	**-1.9**	**MAG**	**-2.5**
ADD2	**-2.2**	PSMA2	-2.6
DPYSL3	**-2.1**	**DYNLRB1**	**-2.1**
RIDA	-2.3	**PACSIN1**	**-3**
DDAH1	**-2.2**	FABP3	-3.6
ALB	**-2.2**	**MAPT**	**-3.2**
PGAM1	**-2.1**	**NEDD8**	**-3.7**
NDUFS4	-2.2	**UCHL1**	**-3.9**
RALA	-2.2	SNCG	-3.1
HSPE1	**-2.7**	HINT1	-3.5
HSPA1A	**-2.2**	**PPP3R1**	**-4.0**
OXCT1	-2.1	SNCA	-4.6
CAP2	**-2.6**	**GDA**	**-5.1**
ME3	**-2.2**	**TXN**	**-6.7**

Tables 1 & 2 showing the upregulated and downregulated proteins in TDP-43 cases as compared to with Alzheimer's disease and healthy controls. The fold change refers to the fold difference when TDP-43 cases are compared to healthy controls. Those proteins highlighted in bold are those which have previously been implicated in disease pathogenesis. Those highlighted in red are those also dysregulated in Laferrière's proteomic study in extracted TDP-43.

The majority of proteins identified are implicated in ribosomal function, RNA transportation and mitochondrial matrix enzymatic function. Proteins essential for cytoskeleton structure were also differentially upregulated in TDP-43 proteinopathies with tubulin alpha-4A increased 7.4-fold compared with controls (whilst not increased in AD).



DISCUSSION

Preliminary proteomic analyses of brain tissue from TDP-43 proteinopathies has identified a number of differentially expressed proteins, providing a starting point for new biomarker development to distinguish different pathological subtypes of FTD during life.

References: Laferrière, F., Maniecka, Z., Pérez-Berlanga, M., Hruska-Plochan, M., Gilhespy, L., Hock, E.-M., … Polymenidou, M. (2019). TDP-43 extracted from frontotemporal lobar degeneration subject brains displays distinct aggregate assemblies and neurotoxic effects reflecting disease progression rates. *Nature Neuroscience*, *22*(1), 65–77.

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