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Proteomic differences in FTLD pathologies

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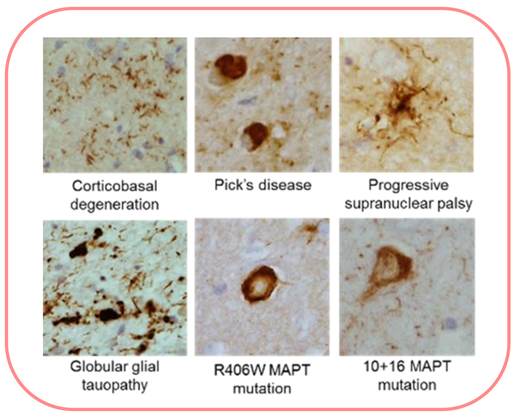
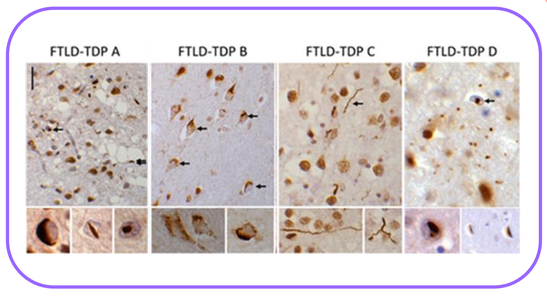
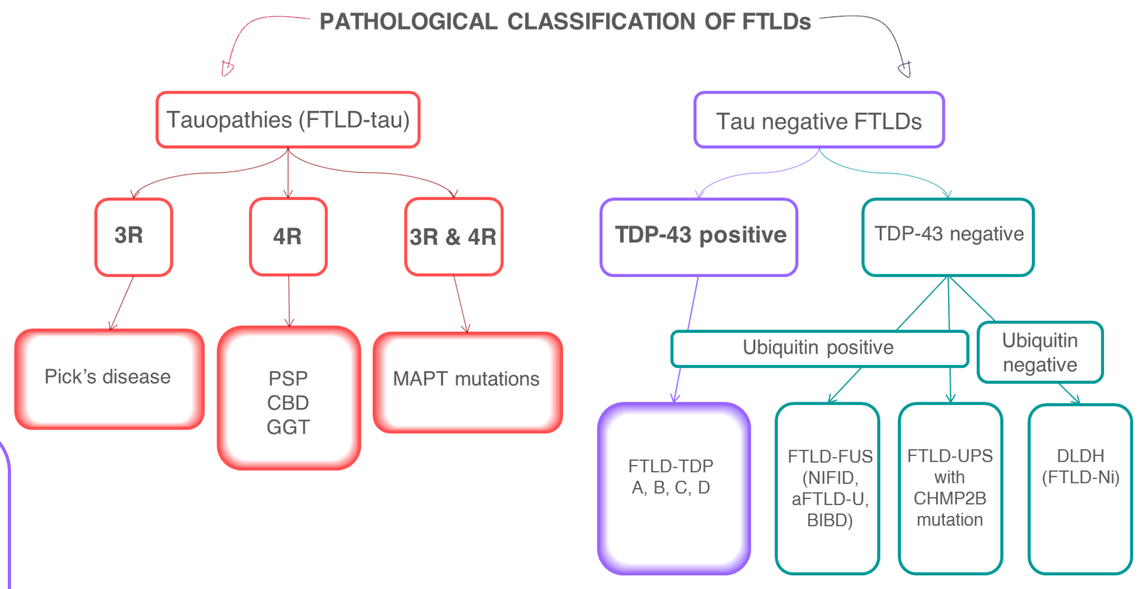
Introduction

Frontotemporal lobar degeneration is a pathologically heterogeneous neurodegenerative disorder associated usually with tau or TDP-43 pathology. Currently, there are no biomarkers able to diagnose the underlying pathology during life. In this study, we aimed to investigate the proteomic differences within and between tau and TDP pathologies.







Pathological diagnosis		Number	Age mean (SD), y	Gender (M%)	Disease Duration mean (SD), y
TAU	PiD	4	68.8 (5.8)	100	9.3 (4.6)
	PSP	4	72.6 (4.5)	100	6.3 (1.2)
	CBD	4	68.9 (2.9)	50	8.6 (1.6)
	GGT (I)	2	80.0 (3.0)	0	4.5 (0.5)
	MAPT 10+16	2	58.5 (7.5)	100	6.5 (0.5)
	MAPT R406W	1	66 (-)	100	11 (-)
	AD	4	76 (7.4)	100	12.5 (4.2)
TDP	TDP A	6	62.7 (7.2)	66.6	7.5 (2.6)
	TDP A *C9orf72*	6	67.3 (4.2)	50	7.0 (1.8)
	TDP B	2	68.1 (1.1)	50	3.1 (0.9)
	TDP C	6	66.7 (11.1)	83	13.8 (5.8)
Healthy control	-	5	82.3 (6.0)	75	-

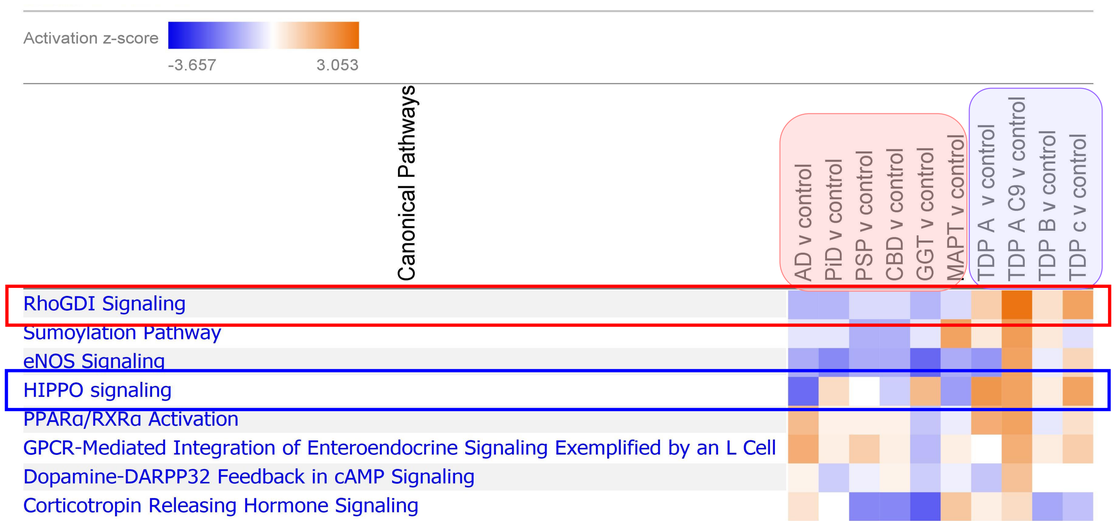
Methods

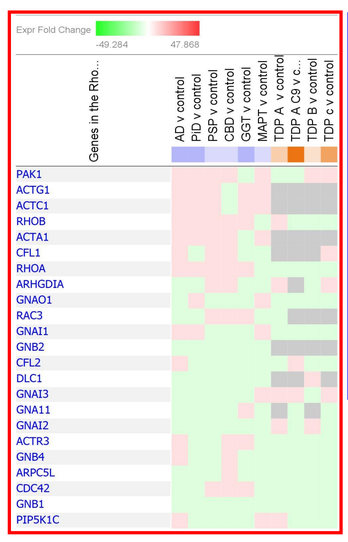
To assess the protein expression in samples, proteins were extracted from the frontal cortex from each case, digested and analysed using Synapt G2-Si High Definition mass spectrometer using 2D online fractionations (4 fractions) to perform quantitative label-free mass spectrometry. Raw data was processed using Progenesis software, normalised and fold-change was calculated compared to controls for each FTLD subgroup. Ingenuity Pathway Analysis (IPA) software was utilised to analyse the pathways and functions represented in both datasets. Pathways and functions were predicted to be activated if they had a positive z-score and were coloured orange. They were predicted to be inhibited if they had a negative z-score and were coloured blue.

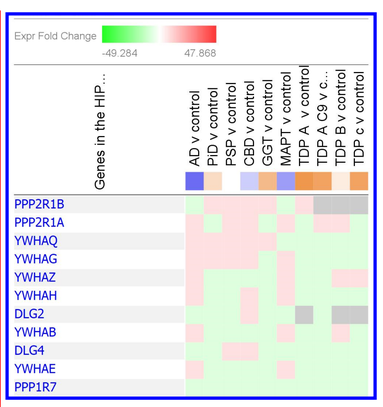
Results

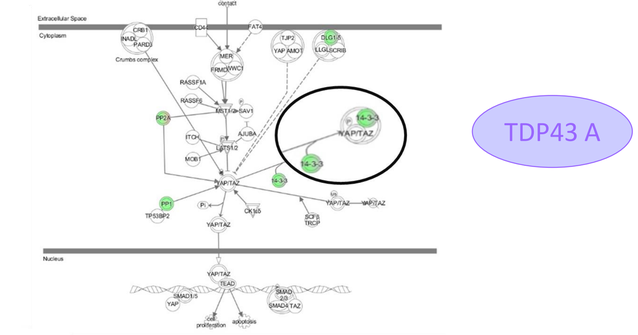
The converging RhoGDI and HIPPO signalling pathways are overexpressed in TDP43opathies compared to tauopathies, possibly indicating different mechanisms of action between tau and TDP43. Canonical pathway differences are present in tauopathies but less so in PSP vs. CBD and MAPT vs. AD.

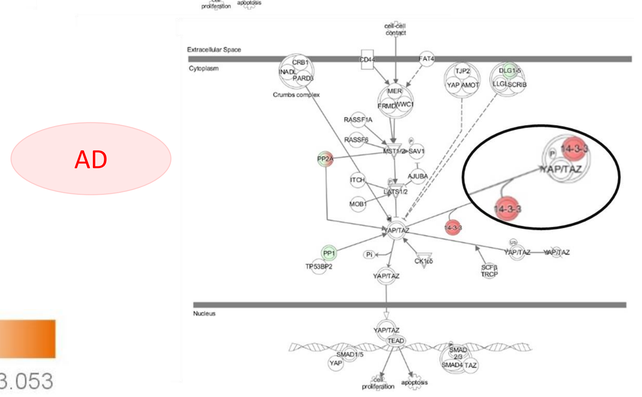
TAU vs TDP43 comparison



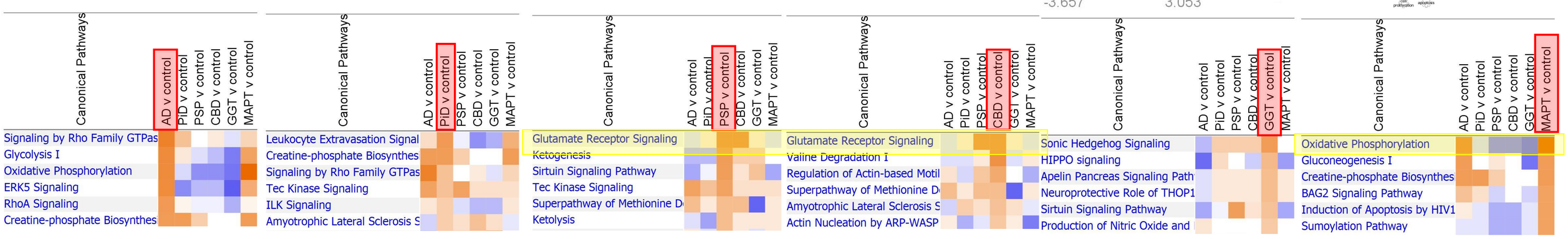








Tauopathies comparison



PSP v CBD

Protein	PSP v CBD	Protein	PSP v CBD
POMT2	5.9	CIDEA	-23.8
SLC39A9	4.4	TXNDC16	-18.8
DBX1	4.1	MRPL40	-13.4
POGLUT3	2.8	TRGV2	-13.1
RBM25	2.5	CMPK1	-10.6
BICDL1	2.4	IRAK3	-9.8
CTNNA3	2.1	BPIFB1	-8.7
SGF29	2.1	CXCL13	-7.6
IRF5	2.1	PCYOX1L	-7.6
RPL10A	2.0	TMEM106A	-5.9

3R v 4R

Protein	4R v 3R	Protein	4R v 3R
CEP170P1	233.1	POMT2	-5.7
IPO7	70.9	ME1	-3.3
SLC1A5	44.1	OPA3	-2.7
FABP5P3	29.4	GPR171	-2.6
PCYOX1L	28.1	SSR2	-2.5
RPS5	20.8	ATP5ME	-2.3
STX1A	20.6	MAP4	-2.3
YARS2	19.1	GABBR1	-2.3
OTOL1	16.1	POGLUT3	-2.2
PCNX4	13.8	SLC4A4	-2.2

Primary tauopathies v AD

Protein	PT v AD	Protein	PT v AD
OTOL1	32.7	IVD	-4.9
HSDL1	14.2	HPRT1	-4.7
SYT5	12.0	SNTA1	-3.8
CLTB	11.3	SLC52A1	-3.4
RPRD1B	10.6	PCYOX1L	-3.4
SLC1A5	9.4	MRPL40	-2.9
AKR1C4	7.9	PCNX4	-2.9
LHPP	7.8	PACS1	-2.9
FABP5P3	7.7	CXCL13	-2.9
LILRB1	5.6	SLC4A10	-2.9

AD v MAPT

Protein	AD v MAPT	Protein	AD v MAPT
SYT5	17.6	CADM4	-4.4
CMPK1	6.5	NIPSNAP2	-3.6
ADAD2	5.6	LRG1	-2.4
SPC24	4.7	SLC4A4	-2.3
TAGLN	4.6	DUSP9	-2.2
CLCN5	4.2	RBM25	-2.0
HEBP1	3.8	CCNA2	-2.0
IVD	3.7	GRIA2	-2.0
CEP170P1	3.4	CCT4	-2.0
NTM	3.4	SIGLEC14	-1.9

Conclusion

This analysis highlights several proteins that could be investigated further as possible biomarkers to distinguish during life tau from TDP43 pathologies as well as tau pathologies from each other.

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