Differential patterns of lysosomal dysfunction are seen in different clinicopathological forms of primary progressive aphasia

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Introduction

Increasing evidence implicates the involvement of the endo-lysosomal and ubiquitin-proteasome systems in neurodegenerative disease.

However, for frontotemporal dementia (FTD), this is largely limited to cellular models in progranulin associated FTD and limited research has explored lysosomal proteins in biological fluids.

Here, we focus on individuals with different variants of FTD subtype, progressive primary aphasia (PPA), each representing a specific clinicopathological syndrome:

- **Logopenic variant** (lvPPA) secondary to Alzheimer's disease
- **Nonfluent variant** (nfvPPA) secondary to a primary tauopathy
- **Semantic variant** (svPPA) secondary to a TDP-43 proteinopathy

Methods

We recruited 36 participants with PPA (13 nfvPPA, 12 lvPPA, 11 svPPA) and 20 healthy controls.

A mass spectrometry panel was used to measure the concentrations of 50 peptides from 18 lysosomal proteins in the cerebrospinal fluid (CSF) of all participants.

Results

Figure 1. Significantly reduced levels of cathepsins B, F, L1 and Z in the CSF of nfvPPA cases compared to controls and lvPPA. CTS (cathepsin). Linear regression adjusting for age and sex (*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001).

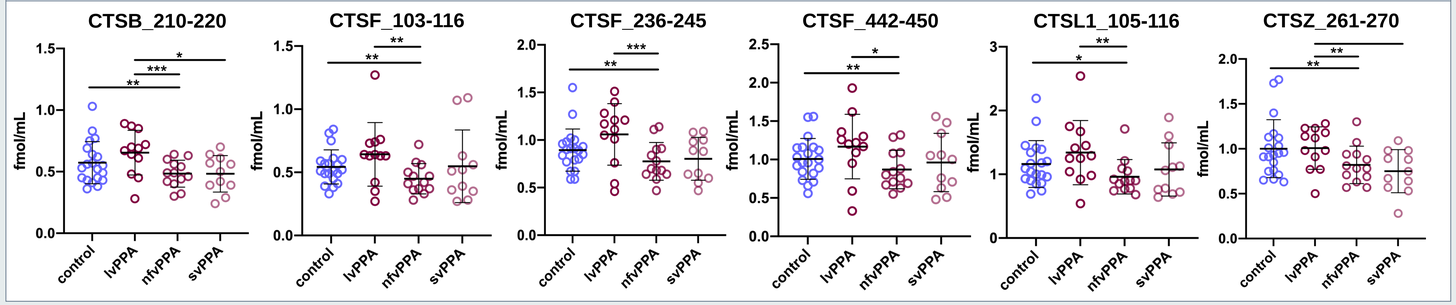


Figure 2. Significantly reduced concentration of lysosomal proteins in nfvPPA vs controls and largely compared to lvPPA. FUCA1 (Tissue alpha-L-fucosidase), LYZ (Lysozyme C), AP2B1 (AP-2 complex subunit beta), APP (Amyloid beta A4 protein), GM2A (Ganglioside GM2 activator), HEXB (Beta-hexosaminidase subunit beta). Linear regression adjusting for age and sex (*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001).

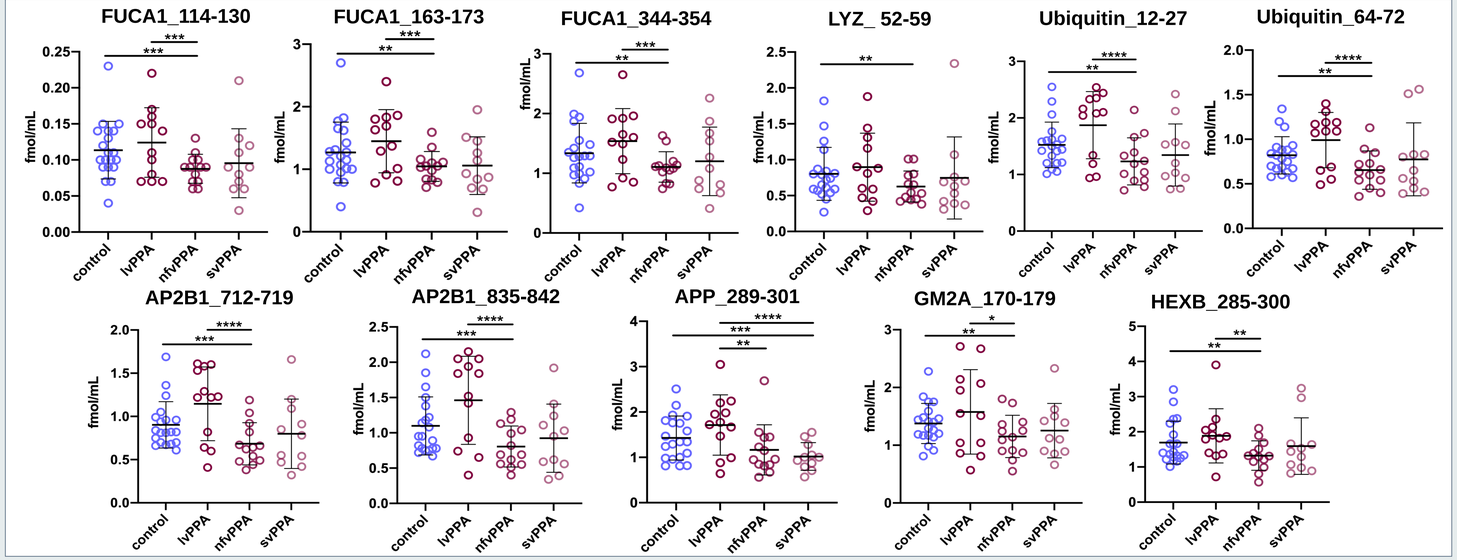
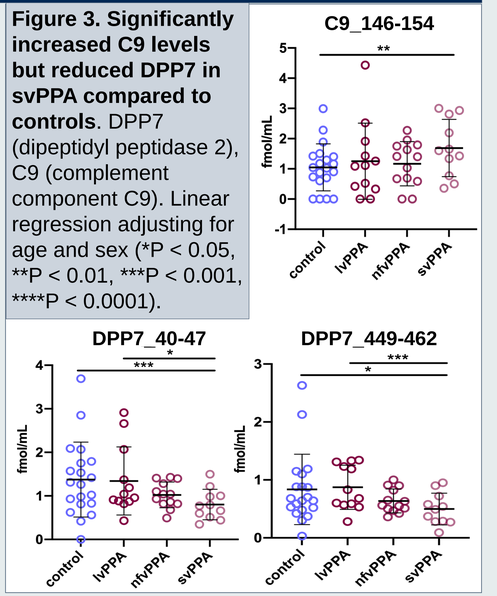


Figure 3. Significantly increased C9 levels but reduced DPP7 in svPPA compared to controls. DPP7 (dipeptidyl peptidase 2), C9 (complement component C9). Linear regression adjusting for age and sex (*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001).



Conclusions

These findings indicate differential lysosomal function in the different variants of PPA, potentially related to the underlying pathology of each variant, where non-AD pathologies are more likely to show decreased lysosomal function in CSF.

This could provide support for diagnosis as well as improving our understanding of the underlying biology of these complex diseases.

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