

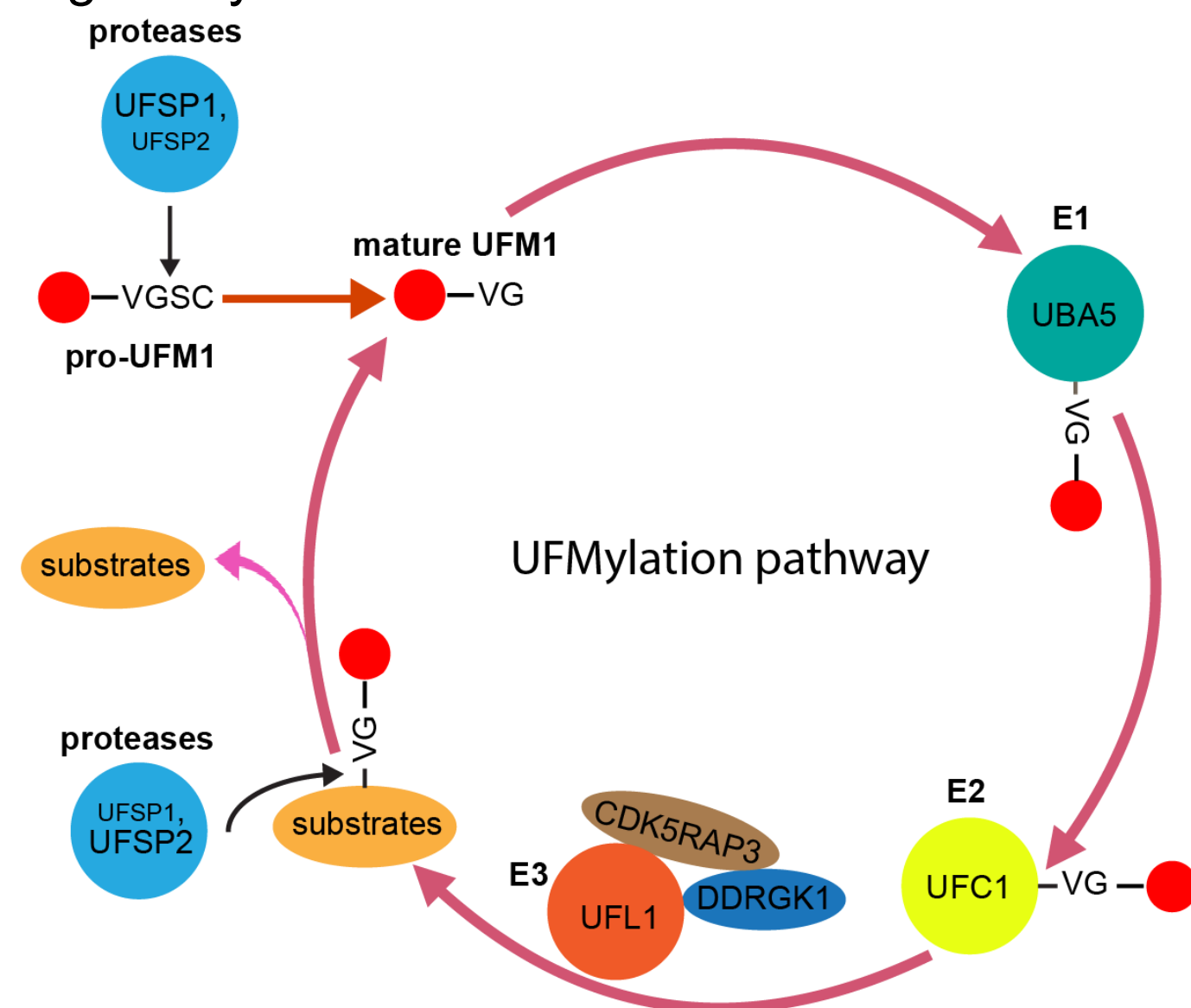
Alterations in the UFMylation Pathway Track with Pathological Tau Burden

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INTRODUCTION

UFM1 is a small ubiquitin-like modifier that has been implicated in neurodevelopmental disorders. Strikingly, the UFM1 cascade has recently been identified as a major modifier of tau aggregation in cells and this was confirmed in animal models with pathological tau. Furthermore, our group recently reported profound changes in the frontal and temporal cortex of Alzheimer's disease (AD) brain compared to neurologically unaffected controls. These changes included the significant increase of conjugated UFM1 and the reduction of soluble UFSP2. In line with the known role of UFSP2 as the UFM1-deconjugation enzyme, both molecular changes were highly negatively correlated with each other.



METHODS

We have developed and validated **novel immunoassays to assess the levels of total UFM1 and UFSP2** and have used these to assess the UFM1 cascade in controls (n=41) and AD (n=72).

We also measured UFM1 and UFSP2 in **frontal cortex** samples from **corticobasal degeneration** and compared to neurologically normal controls. We included cases with frontotemporal dementia characterized by TDP-43 pathology and with diffuse Lewy Body disease, characterized by widespread α -synuclein pathology, as additional non-tauopathy controls (n=20 each). Neuropathological measures were assessed by ELISA to perform correlations with UFM1 and UFSP2

CONCLUSIONS

- We identified marked changes in the UFMylation pathway in human AD brain and in CBD but not in other neurodegenerative diseases.
- Our findings support a modulatory role for the UFM1 cascade in tau pathogenesis within the human brain and underscore the potential of targeting the UFM1 pathway as a promising therapeutic strategy.

FUTURE DIRECTIONS

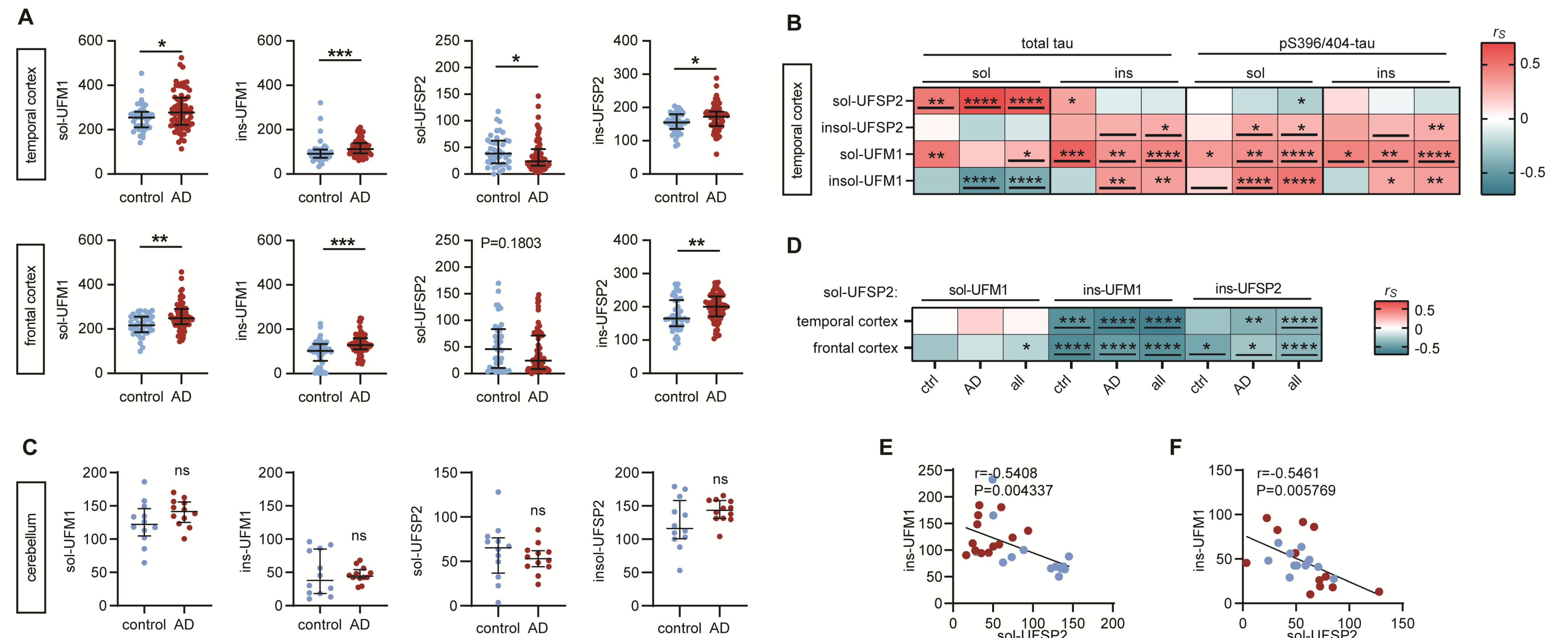
- Identifying UFM1 substrates in human brain, and explore the abnormal UFMylation substrates in AD.
- Investigating the influence of abnormal UFMylation pathway on physiological and pathological tau.

REFERENCES

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RESULTS

ALZHEIMER'S DISEASE



(A) Quantification of soluble (sol) and insoluble (ins) UFM1 and UFSP2 protein levels by MSD ELISA in the frontal and temporal cortex of AD and control cases.

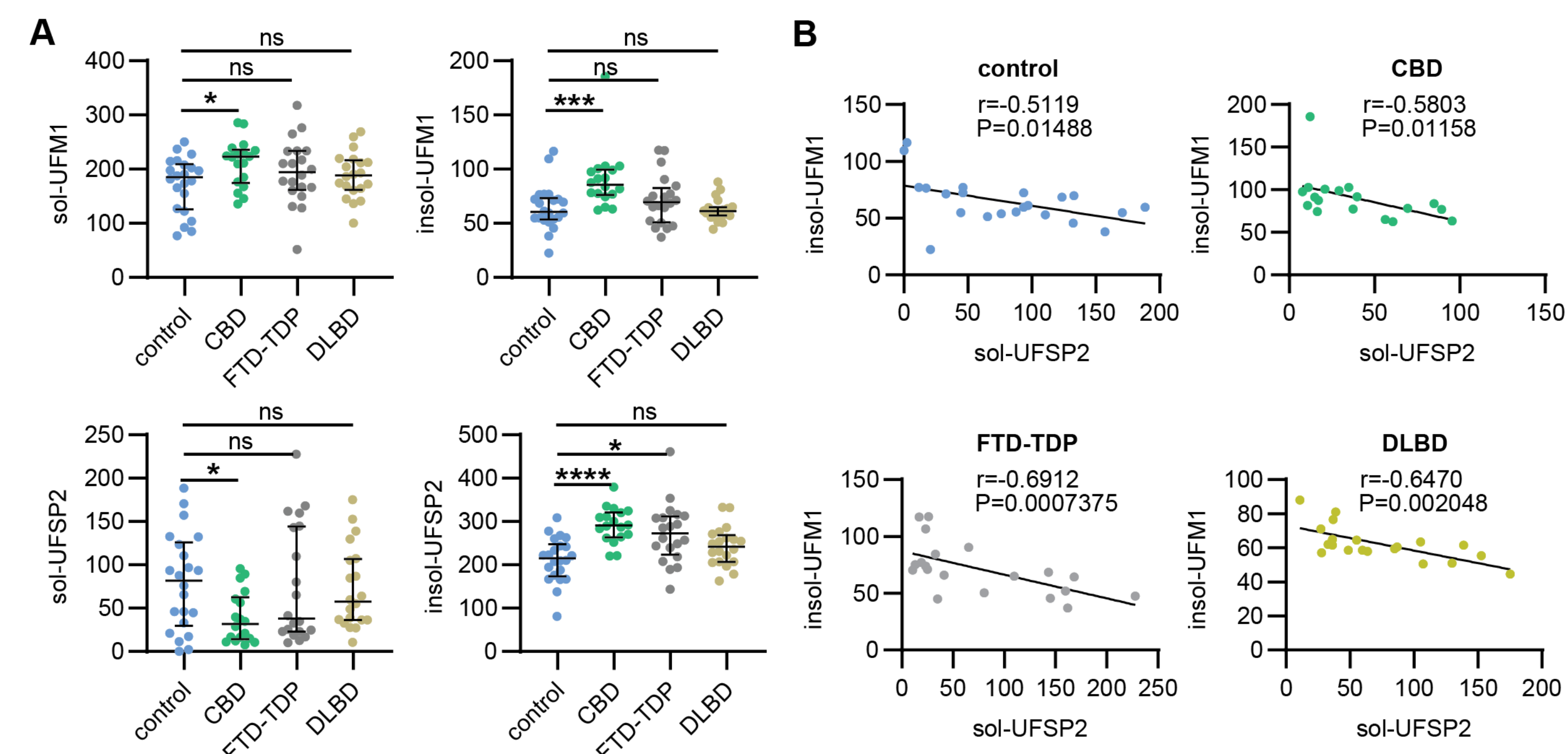
(B) Heatmap of Spearman correlation coefficients (r_s) between UFM1 and UFSP2 protein levels and total tau or pS396/404-tau levels in the temporal and frontal cortex of controls, AD cases, or the combined cohort. Significant correlations confirmed by multivariable linear regression analysis are underlined.

(C) Analysis of MSD ELISA-assessed UFM1 and UFSP2 protein levels in the soluble and insoluble fractions of the cerebellum by disease group. ns, not significant.

(D) Heatmap of Spearman correlation coefficients (r_s) between soluble UFSP2 and UFM1/UFSP2 protein levels in the temporal and frontal cortex. Significant correlations confirmed by multivariable linear regression analysis are underlined.

(E, F) Spearman correlation analyses of MSD ELISA-assessed soluble UFSP2 and insoluble UFM1 protein levels in the same 10 frontal cortex (E) and cerebellum (F) samples demonstrate a strong, significant negative correlation regardless of tau pathology.

CORTICOBASAL DEGENERATION, FRONTOTEMPORAL DEMENTIA (FTD-TDP) AND LEWY BODY DISEASE



(A) Quantification of sol and ins-UFM1 and -UFSP2 levels by MSD ELISA in the frontal cortex across Control, CBD, FTD-TDP, and DLBD cohorts.

(B) Spearman correlation between soluble UFSP2 and insoluble UFM1 in the same cases, showing a strong, significant negative association within the individual cohorts.

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