

Cerebrospinal fluid sTREM2 levels in frontotemporal dementia differ by genetic and pathological subgroup

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Background

- Frontotemporal dementia (FTD) is a clinically and pathologically very diverse disease. Reliable biomarkers of disease onset, intensity and pathology are lacking. Chronic neuroinflammation occurs in FTD, particularly in familial FTD associated with progranulin (*GRN*) mutations. Inflammatory biomarkers are therefore of interest.
- Triggering receptor expressed on myeloid cells 2 (*TREM2*) is a microglial expressed gene. Homozygous mutations produce an FTD-like syndrome and *TREM2* variants increase the risk of Alzheimer's disease (AD) or FTD. When cleaved, soluble TREM2 (sTREM2) is released into the CSF.
- Levels of CSF sTREM2 are raised in AD and correlate with CSF markers of neuronal injury. This has not been explored in FTD.
- We measured CSF sTREM2 levels in individuals with sporadic and familial FTD and healthy controls to assess whether levels differ by clinical subtype of FTD, gene mutation, or underlying pathology. We also explored relationships between CSF sTREM2 and validated CSF neurodegenerative biomarkers: total tau (T-tau), tau phosphorylated at position threonine-181 (P-tau), and amyloid beta 1-42 (Aβ42).

Participants

- 17 healthy controls and 64 individuals with dementia consistent with FTD were recruited from the Specialist Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery or from UCL FTD cohort studies. Those with FTD had either behavioural variant FTD (bvFTD) or a variant of primary progressive aphasia (PPA) leading to five clinical subtypes (Table 1). Ten cases had familial FTD, with mutations in one of three genes: *GRN* (n=3), *C9orf72* (n=3) or *MAPT* (n=4).

Diagnosis	Control	FTD	bvFTD	nvPPA	svPPA	lvPPA	PPA-NOS
Number of participants	17	64	20	16	11	14	3
Male gender N (% group)	6 (54.5)	45 (70.3)	19 (95.0)	9 (56.2)	7 (63.6)	7 (50.0)	3 (100.0)
Age at CSF (years) Mean (SD)	63.7 (6.4)	64.6 (6.5)	63.4 (7.1)	66.9 (5.9)	60.8 (6.0)	66.5 (6.0)	64.6 (5.4)
Age at onset (years) Mean (SD)	n/a	59.5 (6.9)	56.1 (6.7)	62.7 (6.1)	56.1 (5.3)	63.0 (6.7)	61.3 (4.1)
Disease duration at CSF (years) Mean (SD)	n/a	5.1 (3.8)	7.4 (5.6)	4.2 (1.9)	4.7 (2.1)	3.5 (2.0)	3.2 (1.3)

Table 1. Demographics of participants

Methods

- CSF samples were collected by lumbar puncture in polypropylene tubes, centrifuged, the supernatant aliquoted and stored at -80°C until analysis. CSF levels of T-tau, P-tau and Aβ42 were measured using commercially available INNOTEST sandwich ELISAs. CSF sTREM2 levels were measured using an immunoassay (Figure 1).
- CSF sTREM2 levels were compared using multivariable linear regressions adjusted for age, gender and, for disease groups, disease duration, as follows:
 - Between **FTD and control groups**
 - Across **clinical and genetic FTD subgroups** and with controls
 - Between **pathological subgroups** – the FTD group was split by CSF T-tau/Aβ42 ratio into two groups: 1) 'AD biomarker positive' group (ratio >1, AD like CSF and likely AD pathology; n=15); 2) 'AD biomarker negative' group (ratio <1, non-AD like CSF and likely FTLD; n=49); both subgroups were also compared with controls (all ratio <1).
- CSF sTREM2 levels vs. **age, disease duration, and CSF T-tau, P-tau and Aβ42 levels** were assessed in each group and subgroup.

Figure 1. CSF sTREM2 immunoassay

1. Overnight blocking at 4°C

2. Capture antibody (anti-TREM2) Shaking for 1 hour at RT, wash 5x

3. Standards and CSF (diluted 1/4) Shaking for 2 hours at RT, wash 5x

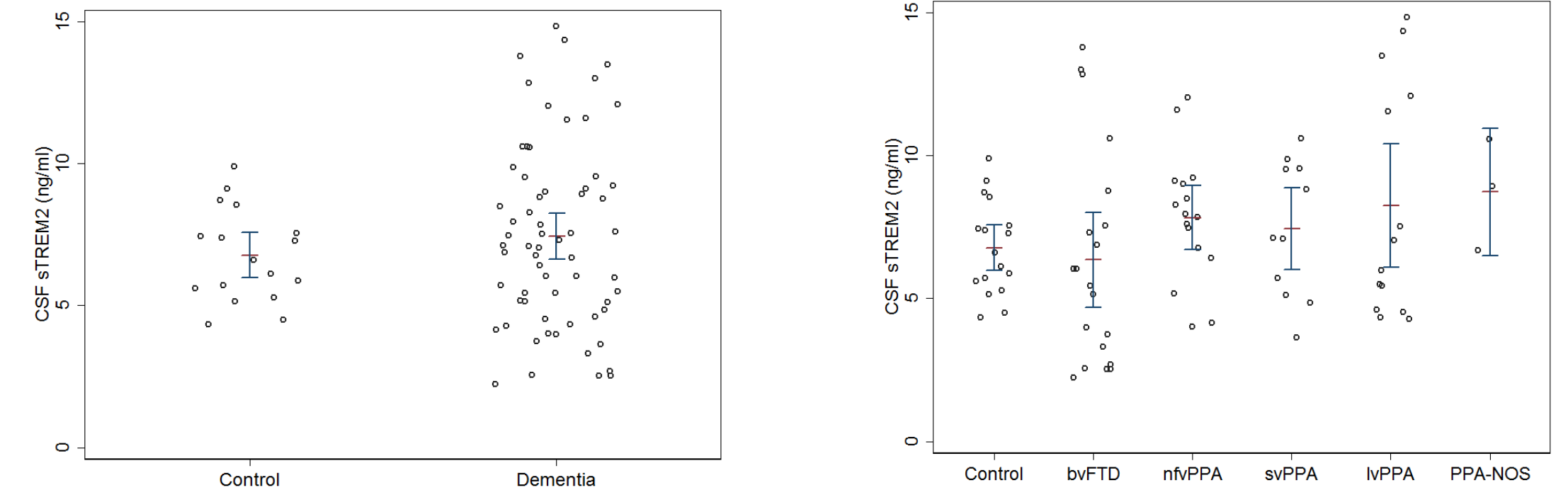
4. Detection antibody (anti-TREM2) Shaking for 1 hour at RT, wash 5x

5. SULFO-TAG antibody Shaking for 1 hour at RT in dark, wash 5x

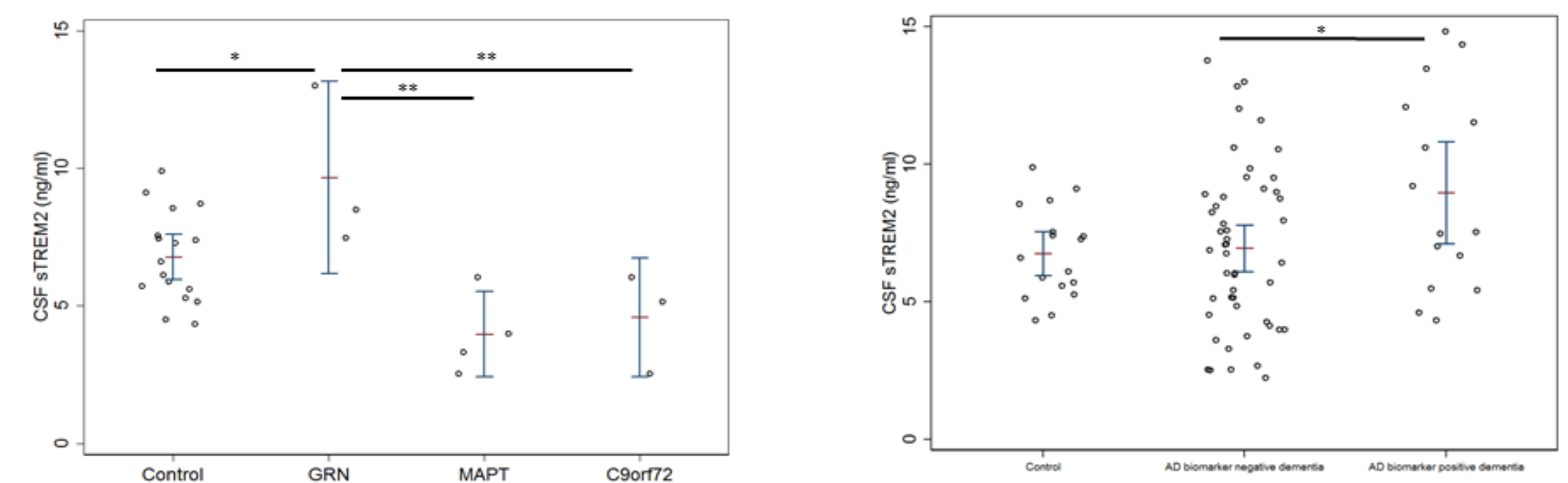
6. Detect electrochemical signal on MSD Sector Imager 6000 and calculate CSF sTREM2 level from standard curve

Results

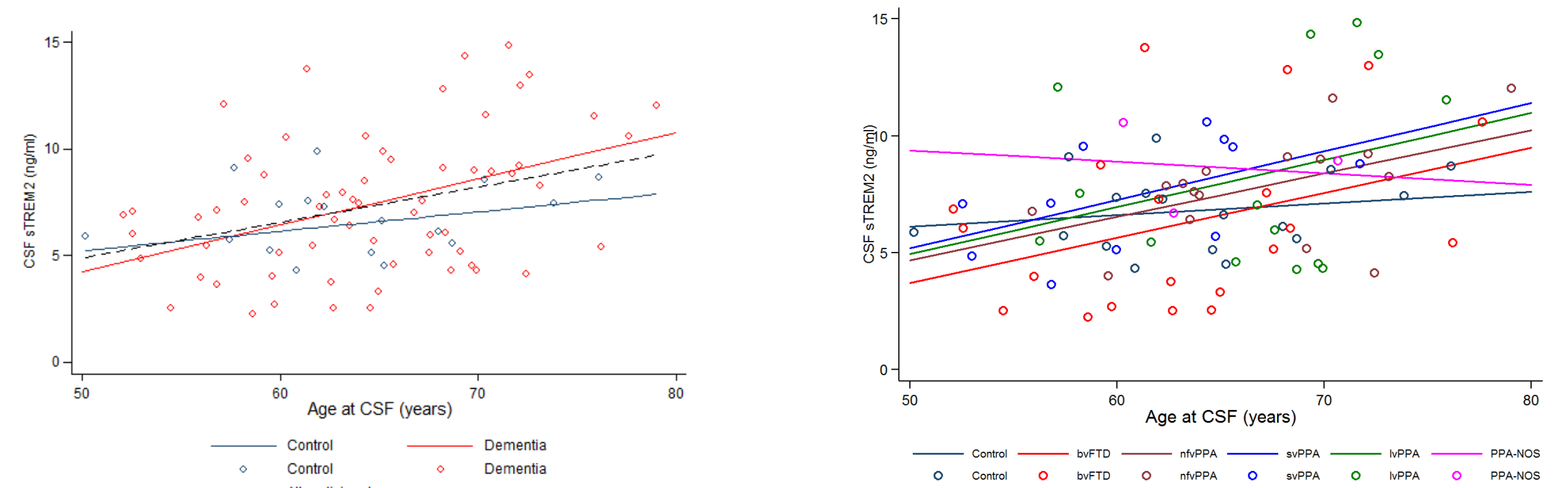
- CSF sTREM2 levels did not differ significantly between FTD and controls (mean (SD)=7.4 (3.2) vs. 6.8 (1.6) ng/ml; $P=0.43$), or between clinical subtypes of FTD:



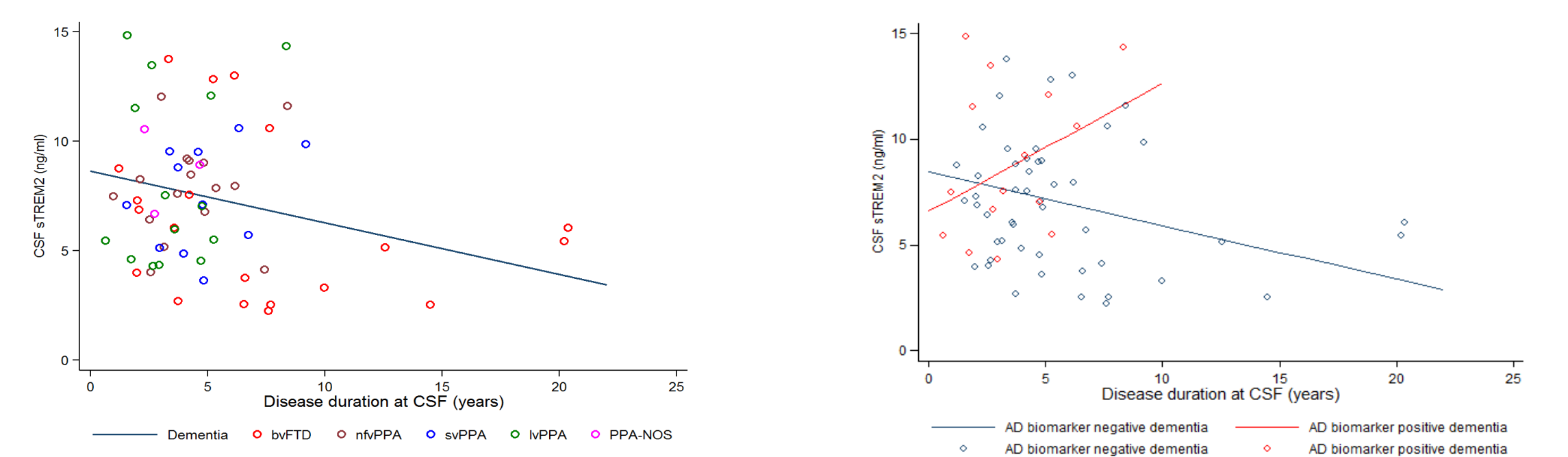
- CSF sTREM2 levels were **higher in *GRN* mutation carriers** than controls (9.7 (2.9) vs. 6.8 (1.6) ng/ml; $P=0.028$) and other mutation groups ($P<0.01$). Levels were also higher in individuals with a clinical diagnosis of FTD but AD like CSF (likely AD pathology) than those with FTD and non-AD like CSF (likely FTLD) ($F_{2,58}=3.77$, $P=0.029$):



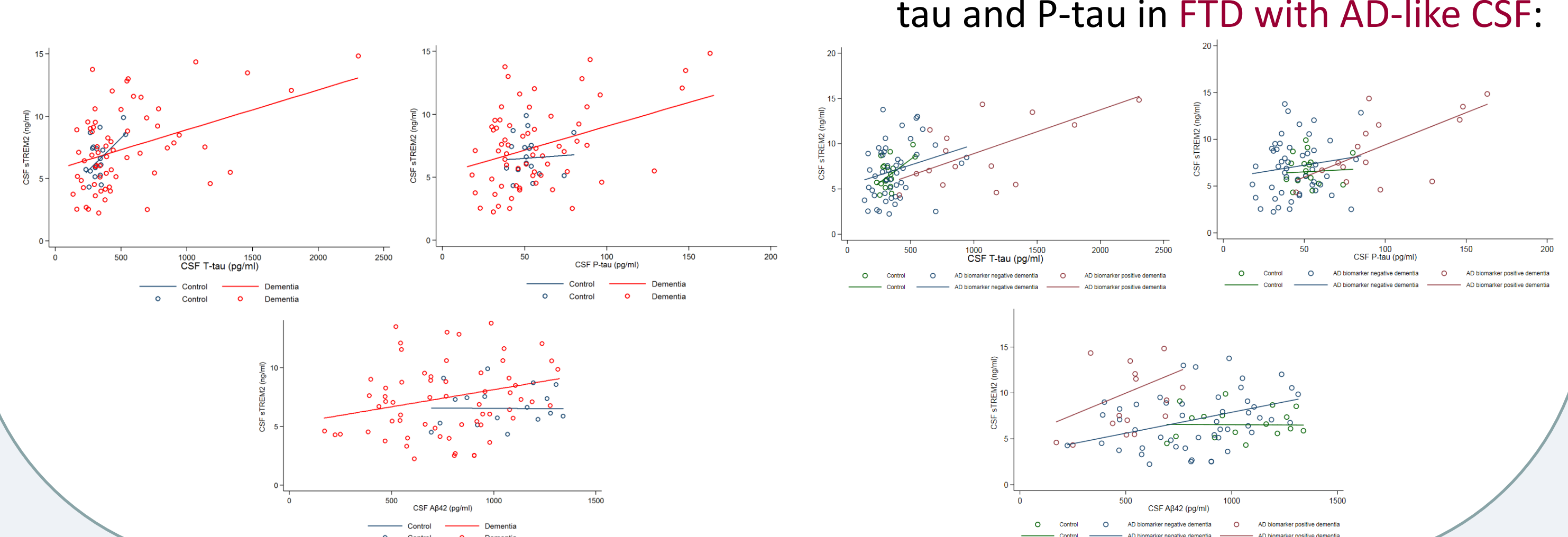
- CSF sTREM2 levels were **positively associated with age** in FTD ($\beta=0.189$, $P<0.001$) and in most clinical subgroups, particularly bvFTD ($\beta=0.271$, $P=0.017$):



- CSF sTREM2 levels were **negatively associated with disease duration** ($\beta=-0.235$, $P=0.025$) particularly in those with non AD-like CSF ($\beta=-0.253$, $P=0.018$):



- CSF sTREM2 levels were **positively associated with CSF T-tau, P-tau and Aβ42 in FTD and T-tau in controls:**



- CSF sTREM2 levels were **positively associated with CSF T-tau and Aβ42 in FTD with non AD-like CSF, and with T-tau and P-tau in FTD with AD-like CSF:**

Conclusion

- CSF sTREM2 levels do not differ between FTD and controls overall, or between clinical subtypes of FTD. However, individuals with FTD due to *GRN* mutations or with FTD due to underlying AD pathology have higher sTREM2 levels, perhaps due to more intense microglial activation.
- CSF sTREM2 levels increase with age in FTD, similar to previous studies of AD, but are lower at longer disease durations. Levels may decrease over time, or lower levels could reflect less intense disease.
- CSF sTREM2 levels correlate with levels of CSF T-tau, a marker of neuronal injury, in FTD, irrespective of underlying pathology. CSF sTREM2 levels may be a biomarker of disease intensity, but this requires longitudinal confirmation.
- Future work: CSF sTREM2 levels are being examined in a large familial FTD cohort with *GRN*, *C9orf72* and *MAPT* mutations to establish if, and when, levels rise pre-symptomatically. This may aid prediction of disease onset and guide early treatment initiation in future clinical trials.