

CSF CHIT1 regulation and activity levels in relation to AD-related biomarkers #0119

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INTRODUCTION

CHIT1, a microglial-derived chitinase, is implicated in neuroinflammatory processes and is increasingly studied in the context of Alzheimer’s disease (AD) (1-3). Elevated enzymatic activity of CHIT1 was observed in the CSF of AD patients (4, 5). The 24 bp duplication (24dup) in the CHIT1 gene, which markedly reduces enzymatic activity (6), offers an opportunity to dissect genetic contributions to CHIT1 expression and function in the CNS. In this context, we studied interactions between CSF CHIT1, its activity, and AD markers, spanning 24dup genotypes and clinical groups.

METHODS

Nineteen CSF samples from AD cases of the Canadian Consortium for Neurodegeneration in Aging (CCNA) and 283 CSF samples from asymptomatic subjects of the PREVENT-AD cohort were analysed using the OLINK HT technology. CSF AD biomarkers Aβ42, total Tau and pTau181 were measured by ELISA (Fujirebio). Chitotriosidase activity was evaluated with the fluorimetric chitinase assay kit from Sigma-Aldrich. Genomic data were generated using de GSA chip from Illumina and imputation yielded over 8.9 million SNPs.

CONCLUSIONS

While CHIT1 did not associate with AD diagnosis, significant associations emerged in the presymptomatic PREVENT-AD cohort, whose participants are at risk of AD due to familial history. The 24dup-dependant correlations with Aβ42, tTau, pTau181 and multiple synaptic markers suggest that genetic variation in CHIT1 modulates its biochemical profile and shapes its relationship with AD pathology.

RESULTS

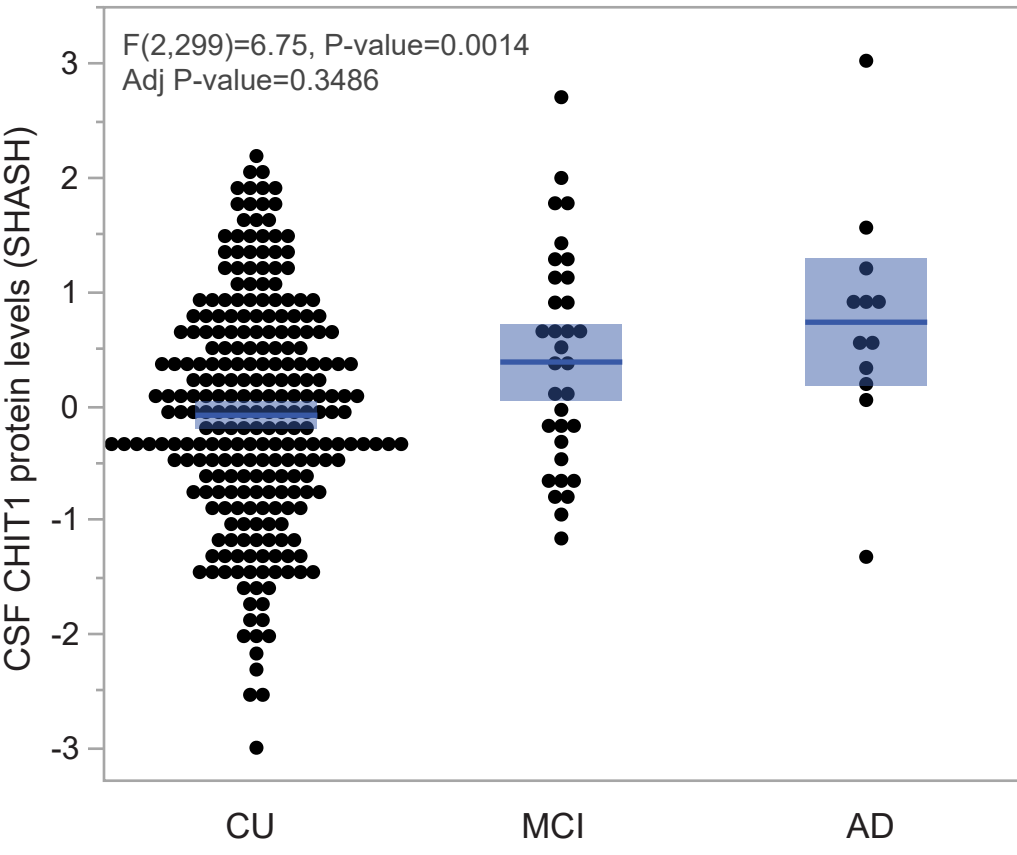


Figure 1. Higher CSF CHIT1 protein levels correlated with aging ($p<0.0001$), male sex ($p<0.0001$) and APOE4 status ($p<0.05$). No significant association with AD diagnosis remained after adjusting for these variables (see figure on the left). CSF samples from the PREVENT-AD cohort and the CCNA cohort were analysed together using the OLINK HT technology.

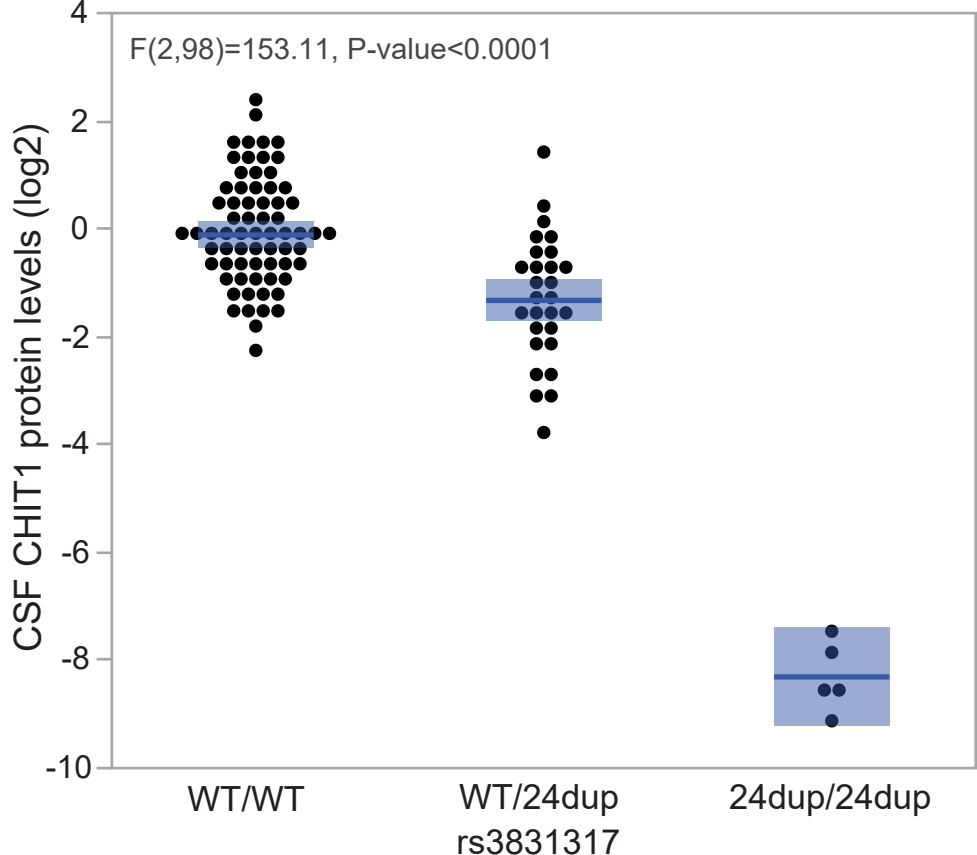


Figure 2. In a *cis*-pQTL analysis, rs3831317 (24dup) showed the strongest association with CSF CHIT1 protein levels ($p=2.7E-18$, data not shown). The 24dup/24dup genotype correlated with minimal CHIT1 protein levels (see figure on the left) and minimal chitotriosidase activity (data not shown). CHIT1 enzymatic activity in WT/WT and WT/24dup individuals strongly correlated with CHIT1 protein levels in the CSF ($p<0.0001$, $R^2=0.91$, data not shown).

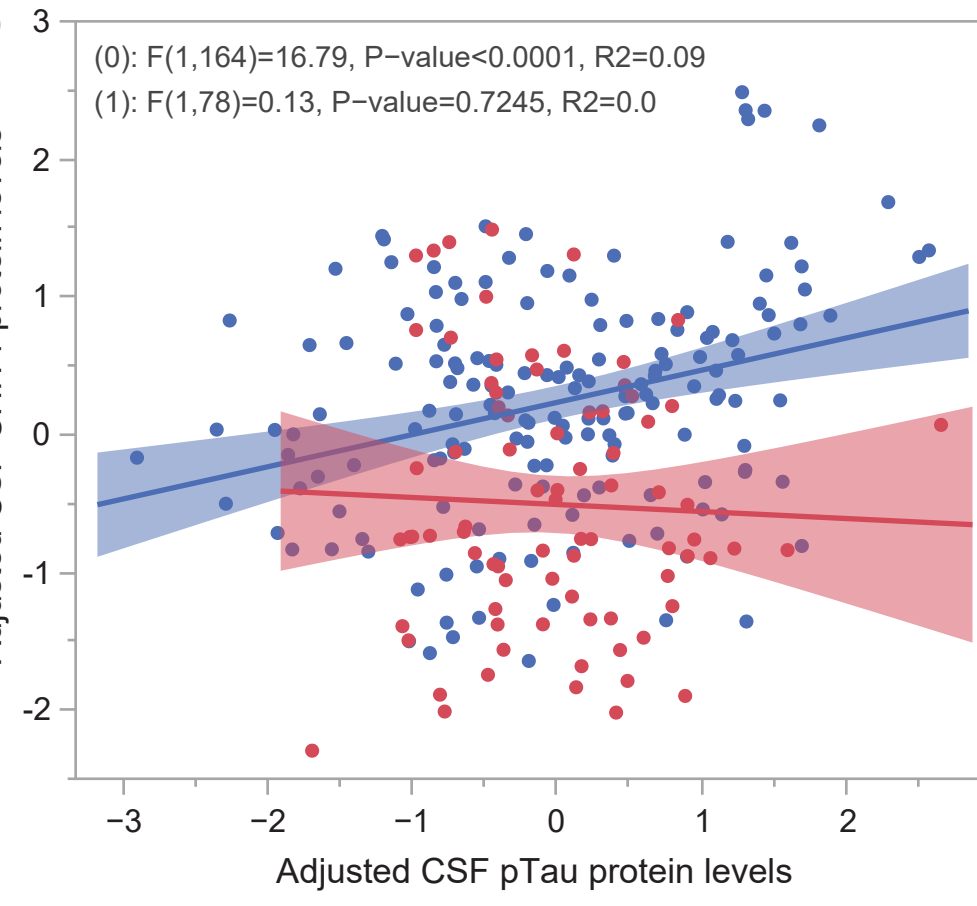
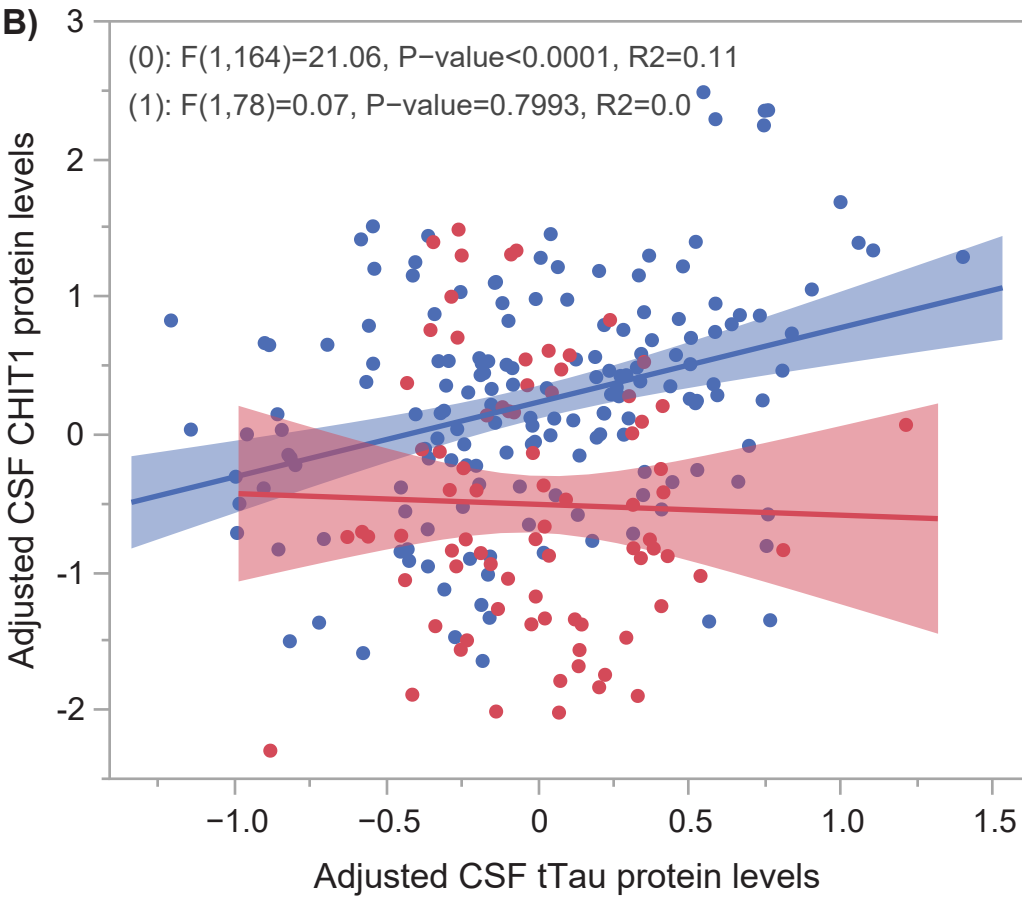
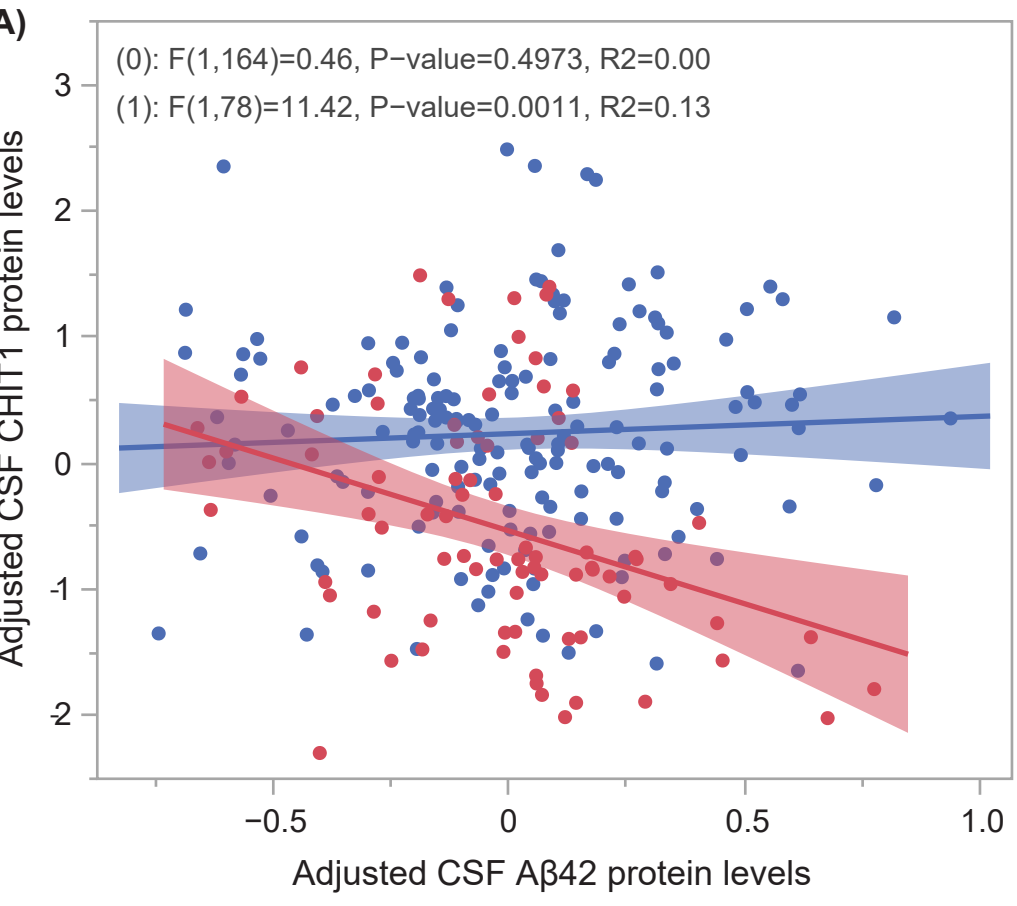


Figure 3. CSF CHIT1 protein levels correlate with AD biomarkers. After stratifying for the 24dup, CSF CHIT1 levels were negatively associated with A) Aβ42 and positively associated with B) tTau and C) pTau181. Results are adjusted for age, sex and APOE4 status.

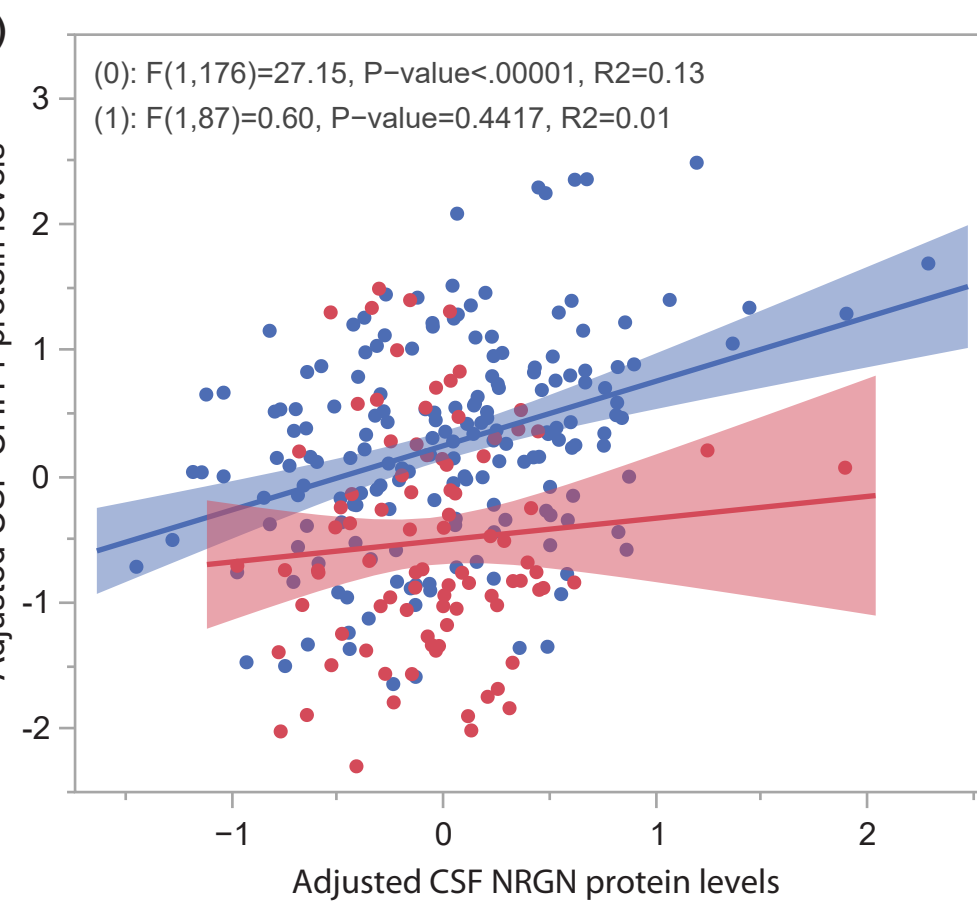
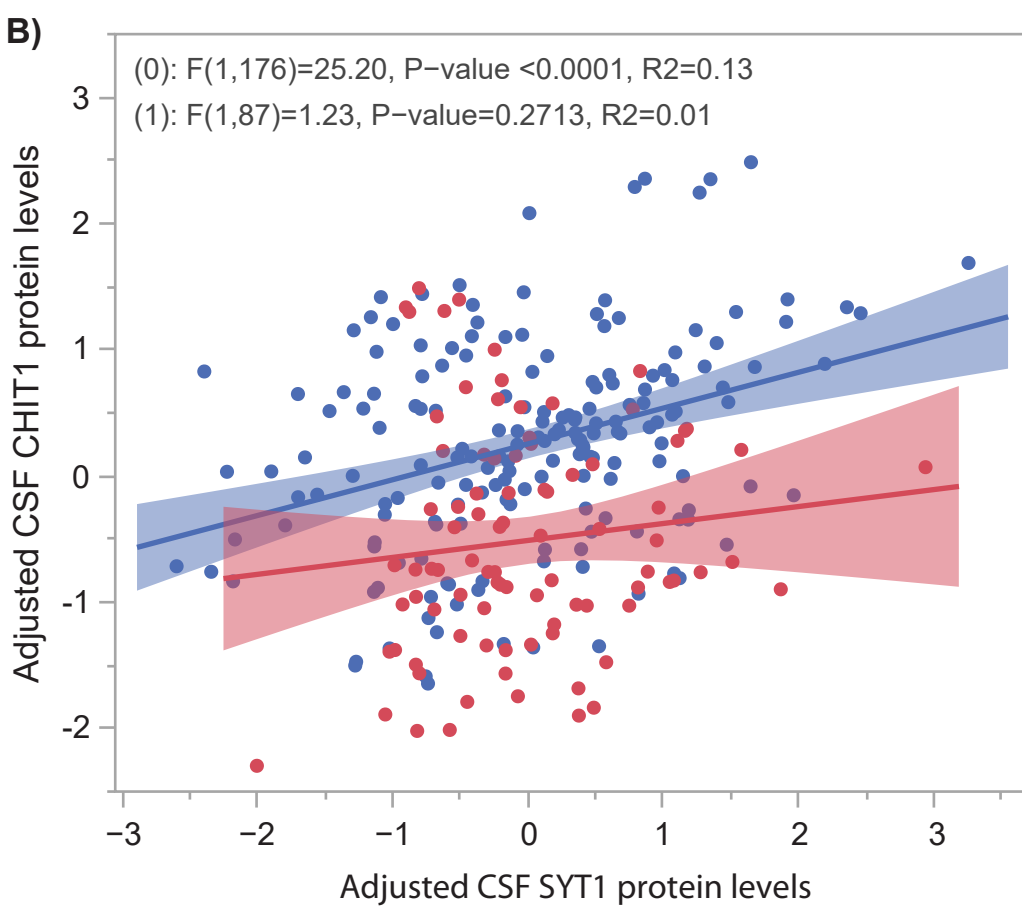
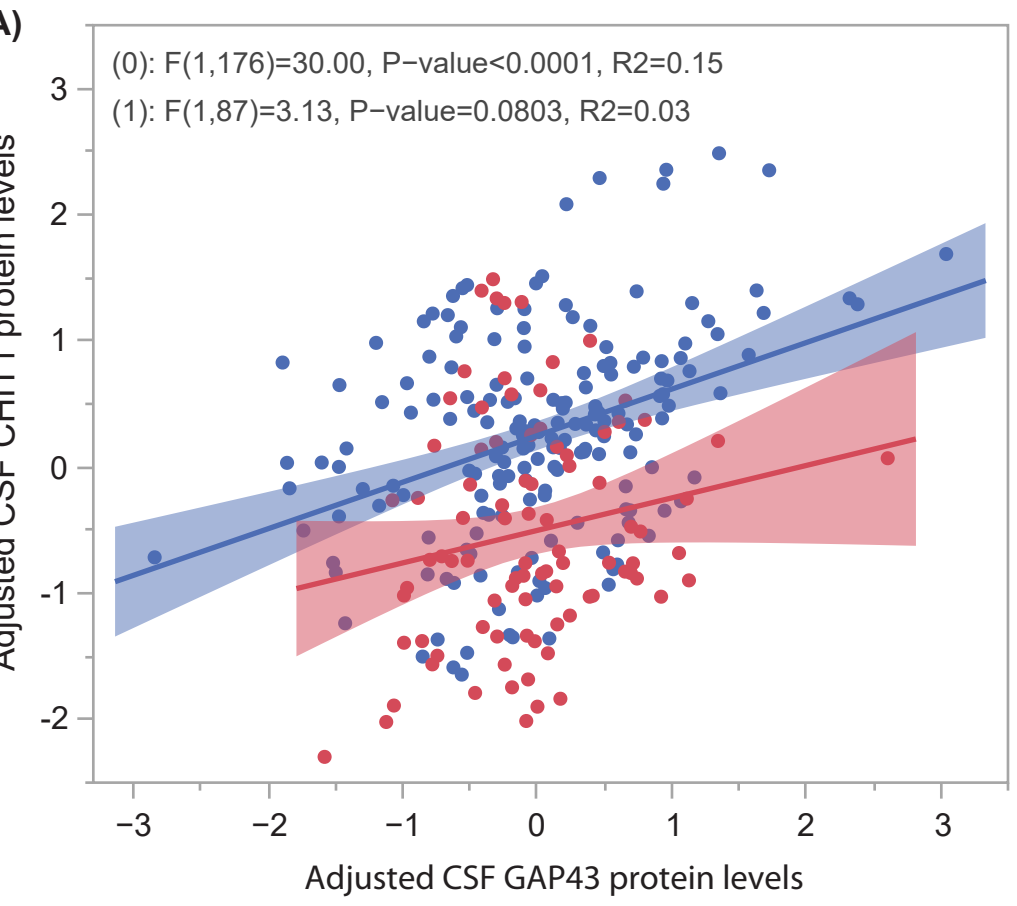


Figure 4. CSF CHIT1 protein levels correlate with synaptic markers. Positive associations were found with the pre-synaptic markers A) GAP43, B) SYT1 as well as with the post-synaptic marker C) NRGN. All proteins were measured with OLINK HT in CSF samples from the PREVENT-AD cohort. Results are adjusted for age, sex and APOE4 status..

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