

Genetic and molecular evidence linking CTSH to Alzheimer’s disease pathophysiology #0228

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INTRODUCTION

Genetics is central to Alzheimer’s disease risk, yet much of this genetic influence remains unexplained. Bellenguez and colleagues found 75 risk loci in the 2022 AD GWAS, 42 of which were previously unknown (1). Of the group, the CTSH gene was one of the most interesting. CTSH is the encoding gene for cathepsin H, a lysosomal cysteine protease enzyme involved in neuroinflammation and diabetes (2-4). Other cathepsins have also been previously associated with neurological and inflammatory diseases’ pathways (5). We sought to further investigate the role of CTSH in the presymptomatic phase of the disease, years before onset.

METHODS

We used 278 CSF samples from the PREVENT-AD group, which has participants predisposed to late-onset AD from family history. In the proteomic analysis, the OLINK-HT technology was employed. CSF AD biomarkers Aβ42, total Tau and pTau181 were measured by ELISA (Fujirebio). Genomic data provided 8.9 million imputed genetic variants from the Illumina GSA chip array.

CONCLUSIONS

Rs2289702 (Gly11Arg) was identified as the most significant SNP in a cis-pQTL analysis and all associations are driven by this variant. Higher levels of CTSH in the T- group have positive associations with tTau, pTau181 and selected synaptic markers, and a negative association with cognitive RBANS attention score, which is consistent with a detrimental effect. These findings position CTSH as a genetically regulated contributor to AD pathophysiology.

RESULTS

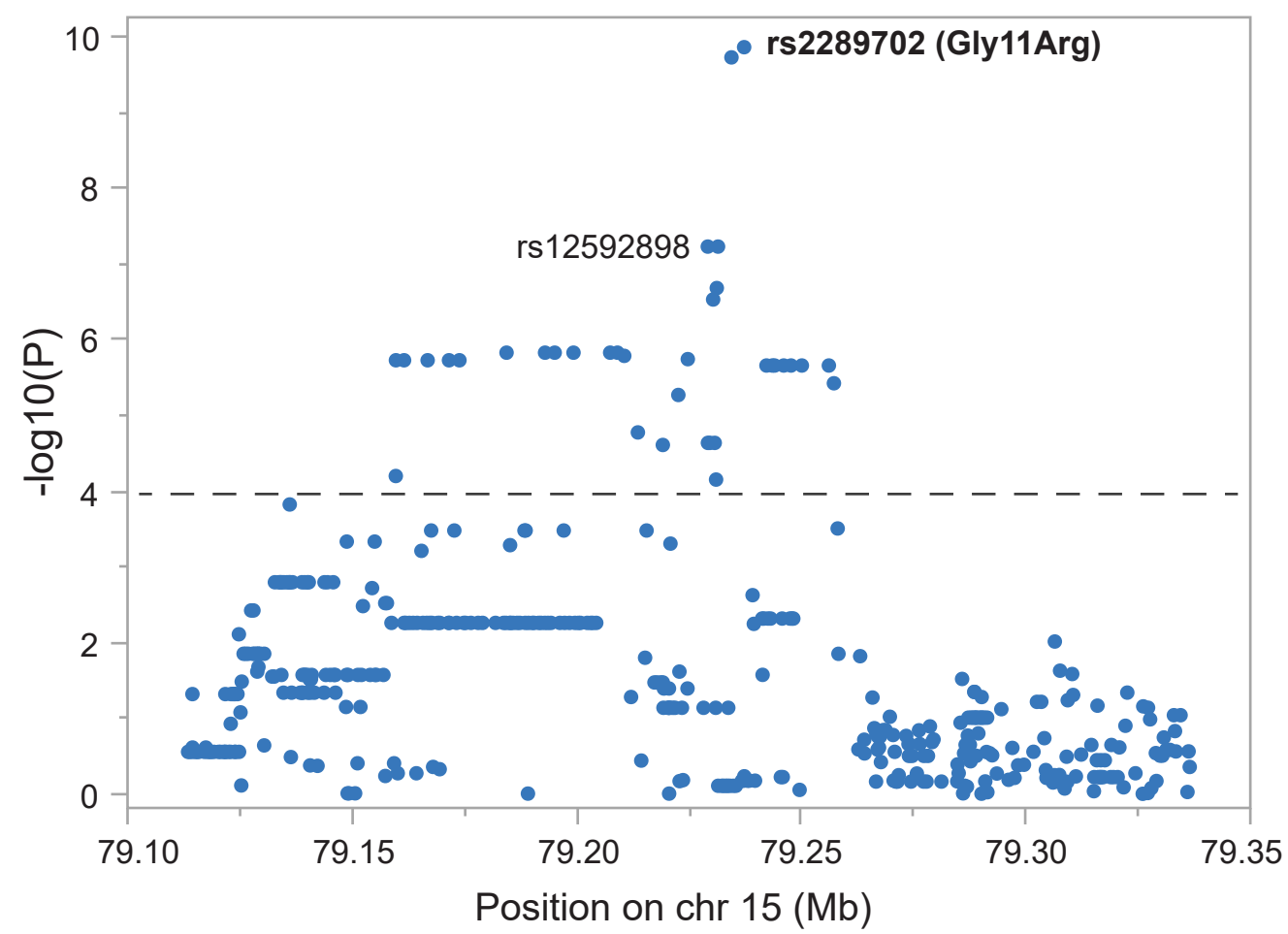


Figure 1. Cis-pQTL analysis spanning CTSH gene region ±100 kb. CTSH protein levels were measured in 81 CSF samples from the PREVENT-AD cohort using OLINK HT technology. Imputed SNPs are located on the x-axis according to their position on chromosome 15 (genome assembly GRCh37). The dotted line represents locus-wide significant threshold. The rs2289702 variant (Gly11Arg) is in strong linkage disequilibrium with the one previously identified by Bellenguez *et al* (rs12592898).

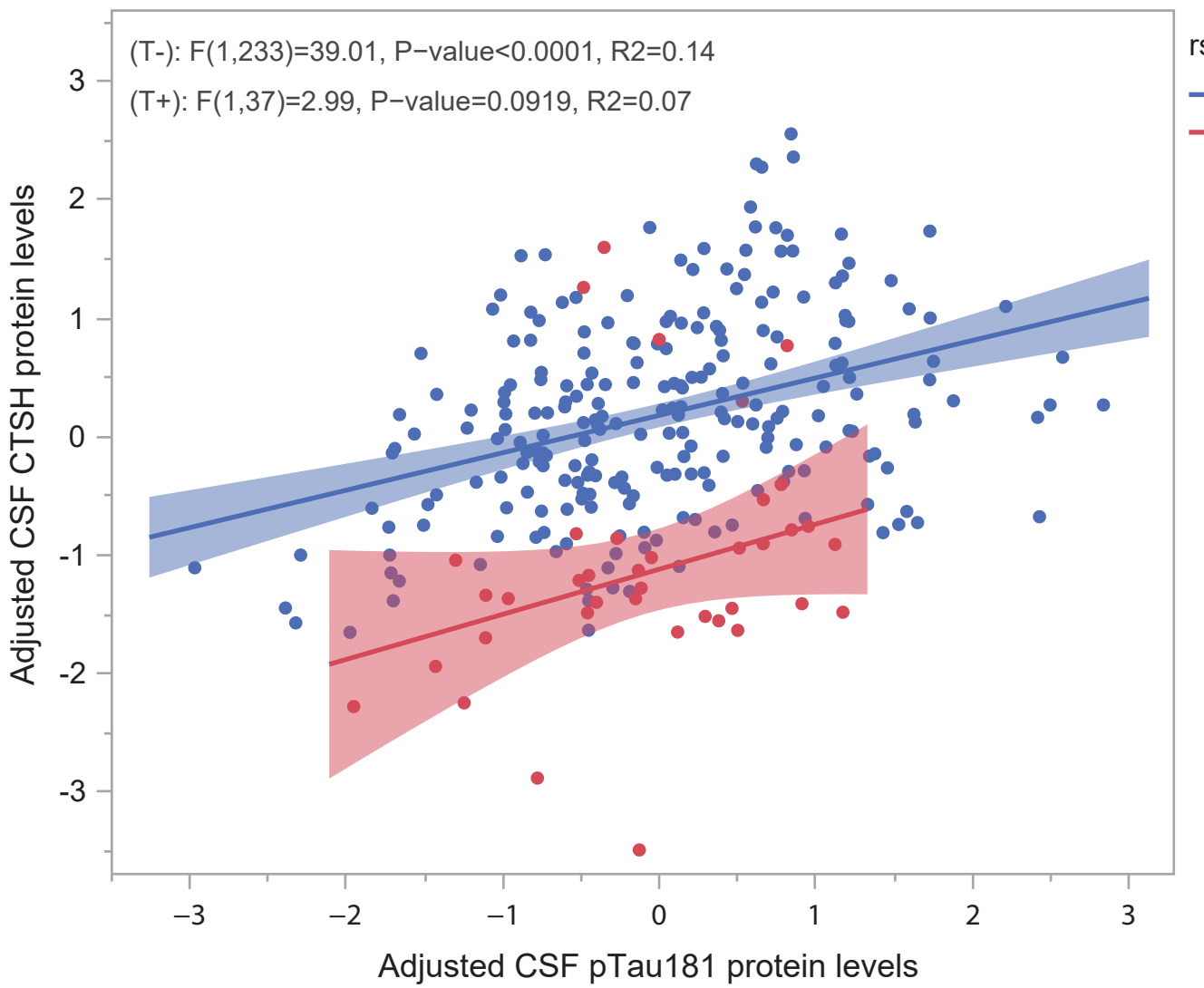


Figure 2. CSF CTSH protein levels compared to AD biomarkers. Protein concentrations were measured using OLINK HT (for CTSH) and ELISA assays for Aβ42, tTau and pTau181. Results are adjusted for age, gender and APOE4 status. Significant associations were found with tTau ($p<0.0001$) and pTau181 ($p<0.0001$, see figure on the left) in the T- group. No significant association was found with Aβ42.

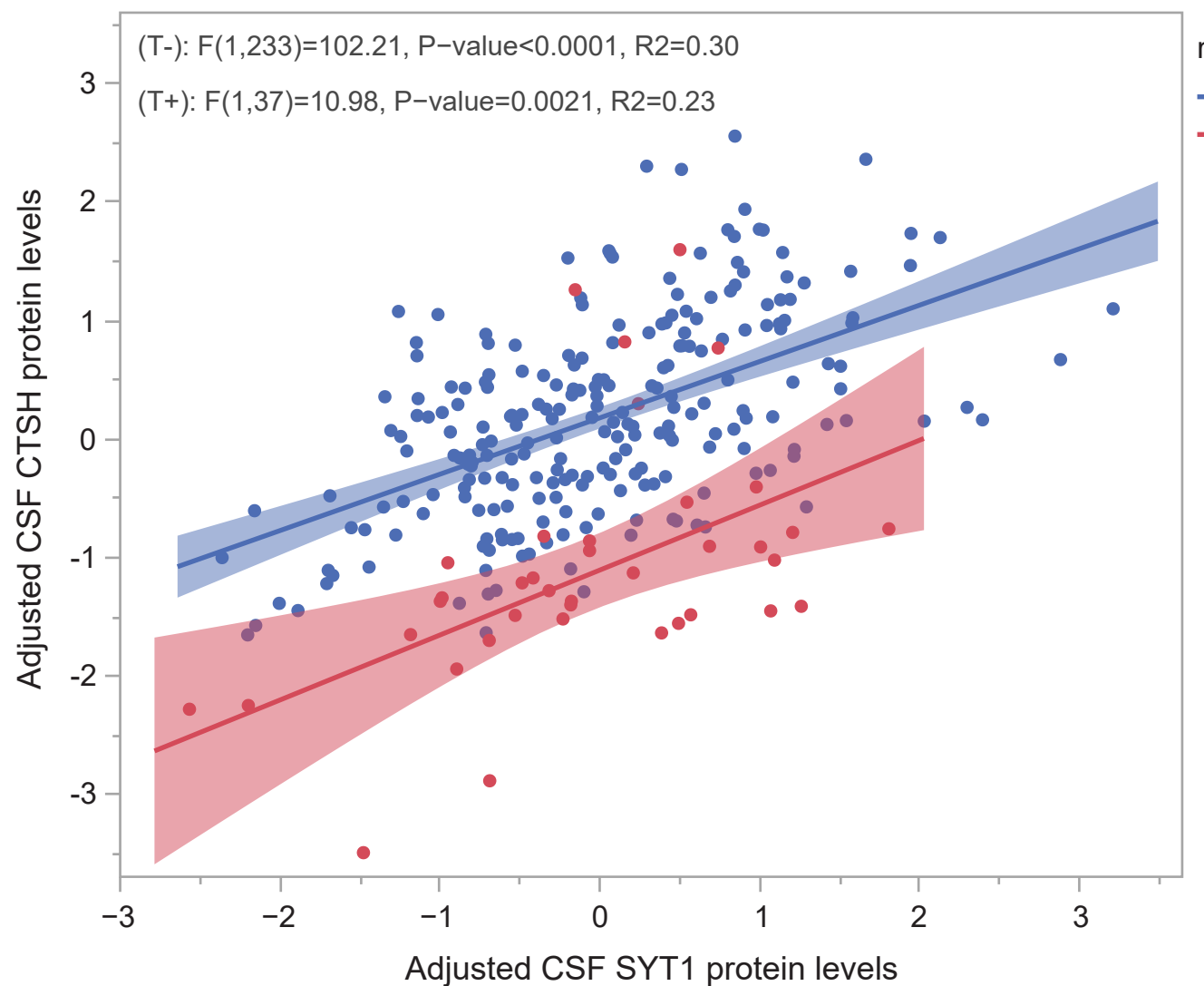


Figure 3. CSF CTSH protein levels compared to synaptic markers. The presynaptic markers GAP43, SNAP25 and SYT1 and the postsynaptic marker NRGN were measured by OLINK HT. The outcomes presented are controlled for age, gender and the presence of the APOE4 allele. In the T- group, significant associations were found for all four markers: GAP43 ($p<0.0001$), SNAP25 ($p<0.0001$), SYT1 ($p<0.0001$, see figure) and NRGN ($p<0.0001$).

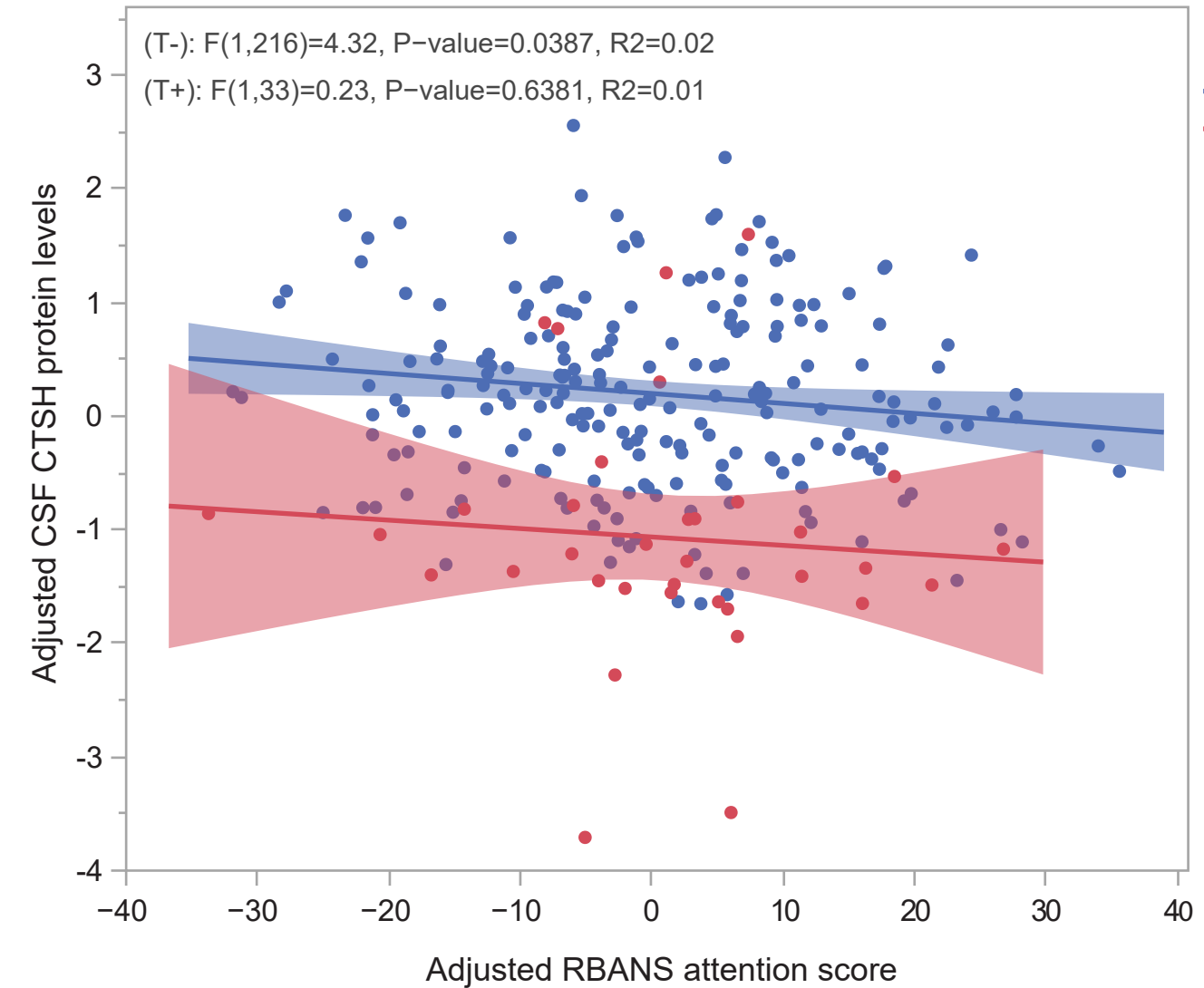


Figure 4. CSF CTSH protein levels in relation to cognitive RBANS score. CSF CTSH levels were measured using OLINK HT and compared with RBANS attention score and RBANS total score. All models include age, sex and APOE4 status as covariates. A significant negative association was observed in the T- group between CTSH and the RBANS attentions score ($p=0.0387$, see figure on the left). No significant association was found with the RBANS total score.

REFERENCES

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