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# CSF tau microtubule-binding region identifies pathological changes in primary tauopathies

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**Supplementary Information**

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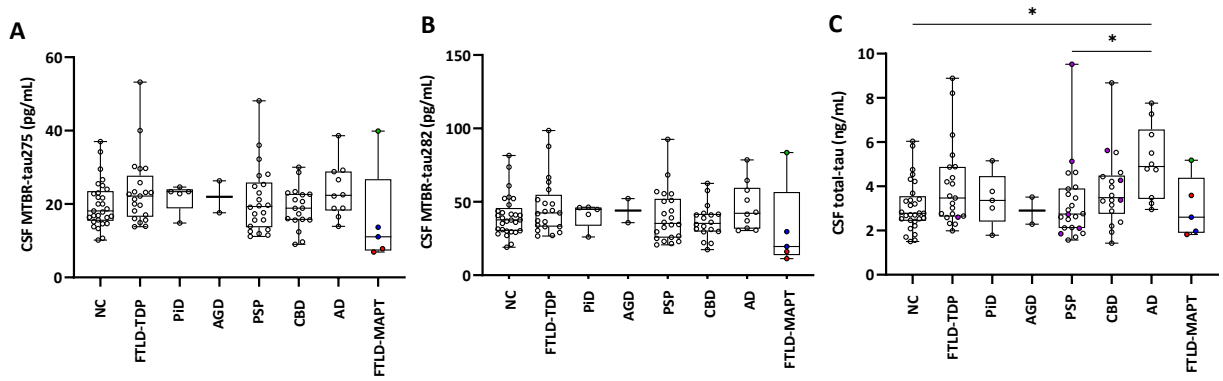
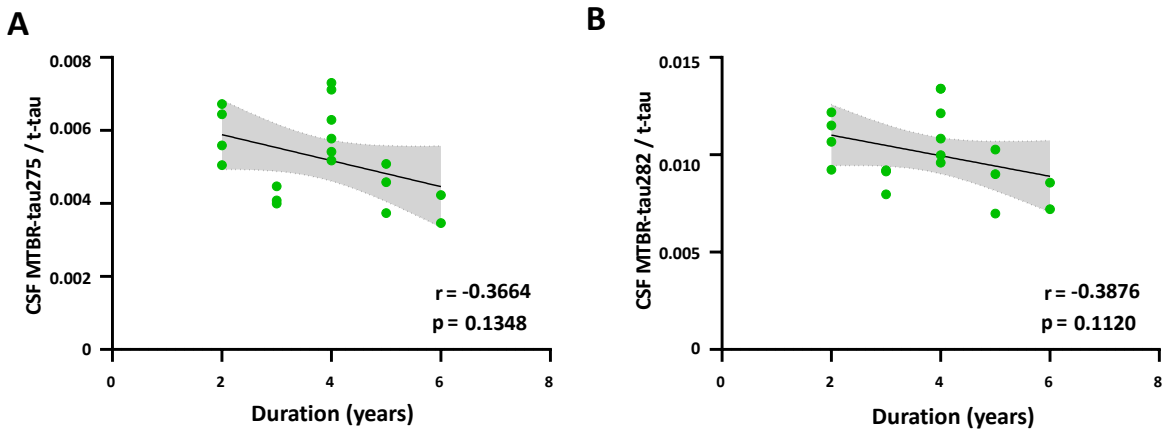
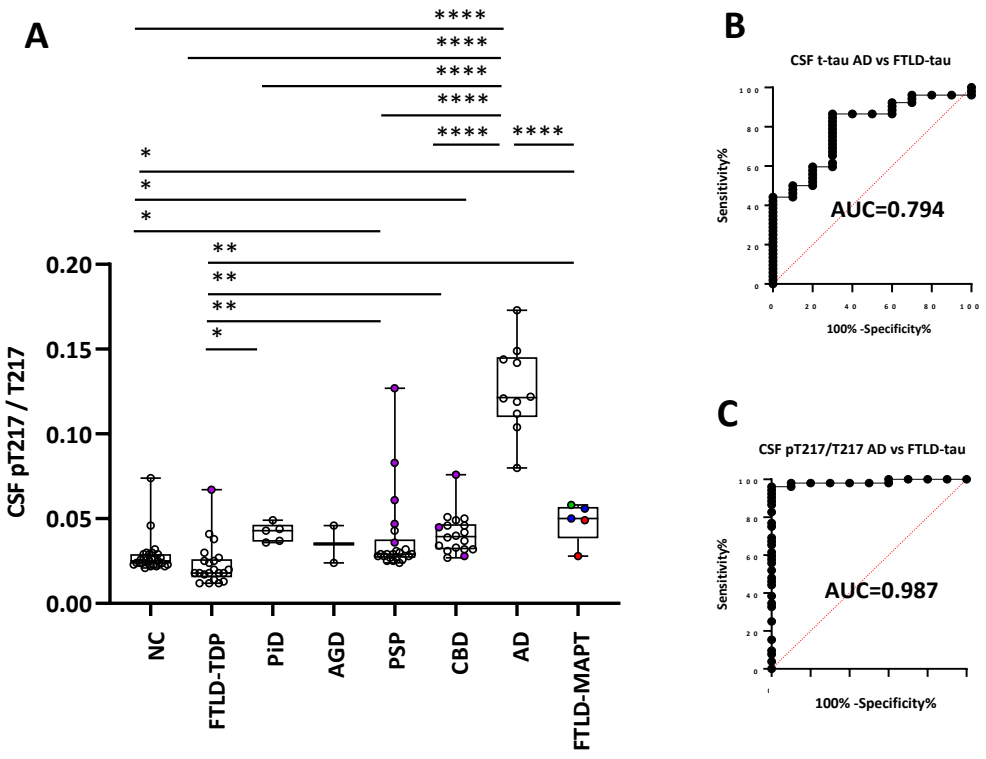



**Supplementary Fig 1. CSF MTBR-tau and t-tau concentrations do not reflect CBD and FTLD-MAPT pathologies.** CSF MTBR-tau275 (A) and MTBR-tau282 (B) concentrations do not change with tauopathies (n=112 total including 29 NC). FTLD-MAPT includes P301L (red, n=2), R406W (blue, n=2) and S305I (green, n=1). CSF t-tau (C) increased in autopsy confirmed AD (n=10) compared to NC (n=29) and PSP (n=22, $p<0.05$). Significance in statistical test: *$P<0.05$. The box plots show the minimum, 25 percentile, median, 75 percentile, and maximum. Differences in biomarker values were assessed with one-way ANOVAs. A two-sided $p<0.05$ was considered statistically significant and corrected for multiple comparisons using Benjamini-Hochberg false discovery rate (FDR) method with FDR set at 5%. NC: normal control, FTLD-TDP: frontotemporal lobar degeneration with TAR DNA-binding protein, PiD: Pick's disease, AGD: argyrophilic grain disease, PSP: progressive supranuclear palsy, CBD: corticobasal degeneration, AD: Alzheimer's disease, FTLD-MAPT: frontotemporal lobar degeneration with *MAPT* mutation.

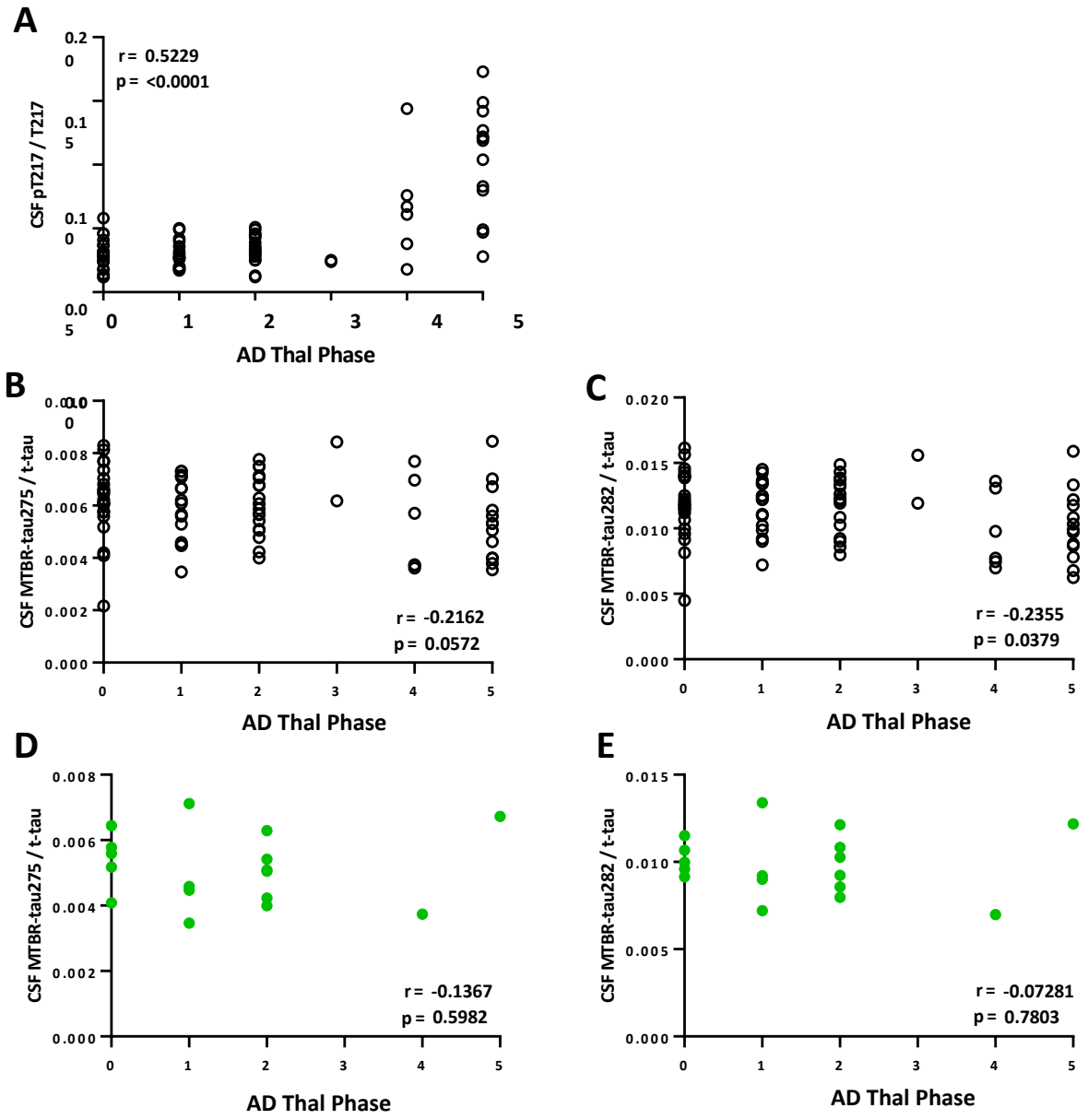



**Supplementary Fig. 2. CSF MTBR-tau/tau correlates with disease duration in CBD.** CSF MTBR-tau275/t-tau (A) and MTBR-tau282/t-tau (B) negatively correlates with duration of the disease in CBD (i.e. interval between age of onset and CSF collection, n=18, Spearman r=-0.37, p=0.13 and r=-0.39, p=0.11, respectively). Gray shadow represents 95% confidential intervals for linear regression. CBD: corticobasal degeneration.

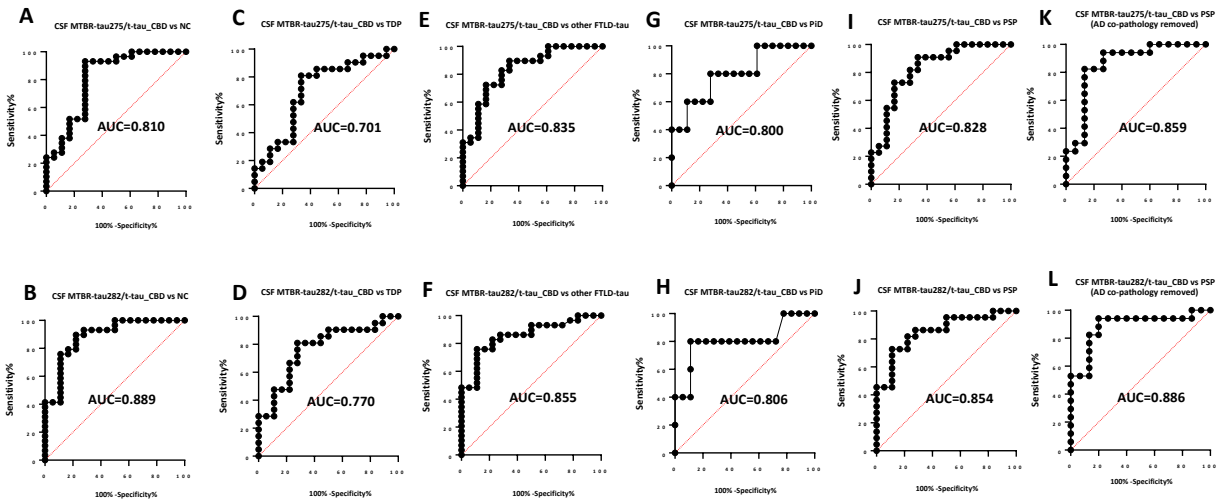



**Supplementary Fig. 3. CSF pT217/T217 identifies AD from other tauopathies.** (A) CSF pT217/T217 increased in AD (n=10) compared to NC (n=29), FTLD-tau (i.e. PiD (n=5), PSP (n=22), CBD (n=18), and FTLD-MAPT (n=5)), and FTLD-TDP (n=21) ($p<0.0001$). PSP, CBD, and FTLD-TDP with AD co-pathology (filled purple, n=9) had higher CSFpT217/T217. FTLD-MAPT includes P301L (red, n=2), R406W (blue, n=2) and S305I (green, n=1). CSF pT217/T217 decreased in FTLD-TDP (n=21) compared to PiD (n=5), PSP (n=22), CBD (n=18) and FTLD-MAPT (n=5, $p<0.05$-0.01). CSF t-tau (C) and CSF pT217/T217 (D) can distinguish AD (n=10) from FTLD-MAPT (n=5) with AUC=0.794, 0.987, respectively. Differences in biomarker values were assessed with one-way ANOVAs. A two-sided $p<0.05$ was considered statistically significant and corrected for multiple comparisons using Benjamini-Hochberg false discovery rate (FDR) method with FDR set at 5%. Significance in statistical test: ****P<0.0001, **P<0.01, *P<0.05. NC: normal control, FTLD-TDP: frontotemporal lobar degeneration with TAR DNA-binding protein, PiD: Pick's disease, AGD: argyrophilic grain disease, PSP: progressive

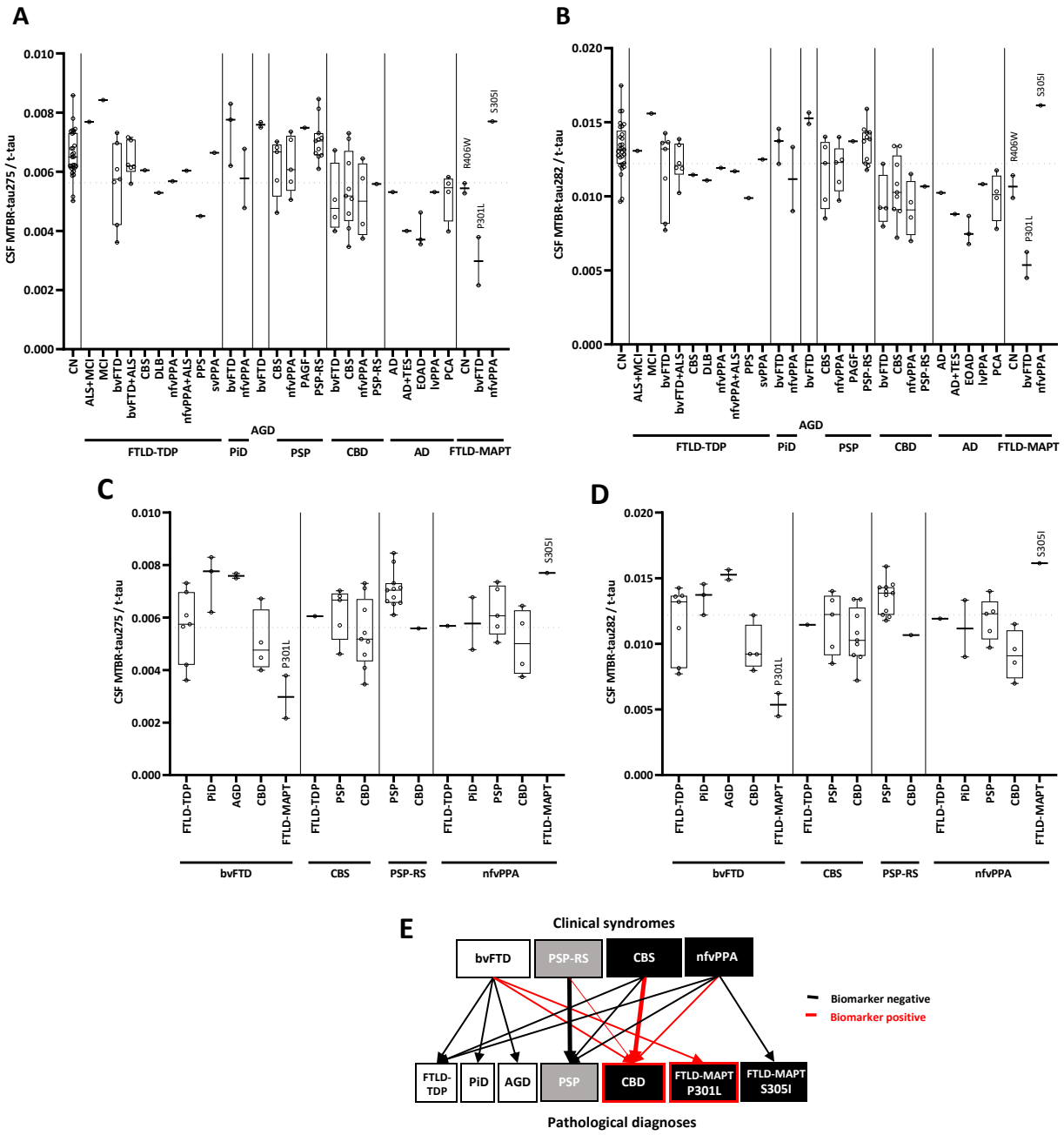
supranuclear palsy, CBD: corticobasal degeneration, AD: Alzheimer's disease, FTLD-MAPT: frontotemporal lobar degeneration with *MAPT* mutation. AUC: area under the curve.




**Supplementary Fig. 4. CSF MTBR-tau275/t-tau and MTBR-tau282/t-tau do not correlate with amyloid pathology in primary tauopathies.** (A) CSF pT217/T217 positively correlates with AD Thal Phase (Spearman r=0.52, p<0.0001). CSF MTBR-tau275/t-tau (B, D) and CSF MTBR-tau282/t-tau (C, E) do not correlate with AD Thal Phase measured in autopsied brains of all tauopathy cohort (B, C, n=79) or CBD only (D, E, n=17).




**Supplementary Fig. 5. ROC curves for 4R specific CSF MTBR-tau to distinguish CBD from control and other tauopathies.** CSF MTBR-tau275/t-tau (A, C, E, G, I, K) and MTBR-tau282/t-tau (B, D, F, H, J, L) can distinguish CBD from NC (A, B), FTLD-TDP (C, D), FTLD-tau (i.e. PSP, PiD and AGD, E, F), PiD (G, H), and PSP (I, J). AUC improves when AD co-pathology cases are excluded from CBD and PSP (K, L). NC: normal control, FTLD-TDP: frontotemporal lobar degeneration with TAR DNA-binding protein, PiD: Pick's disease, AGD: argyrophilic grain disease, PSP: progressive supranuclear palsy, CBD: corticobasal degeneration, AD: Alzheimer's disease, FTLD-MAPT: frontotemporal lobar degeneration with *MAPT* mutation. AUC: area under the curve, ROC: receiver operating characteristic.




**Supplementary Fig. 6. Retrospective clinical syndromes and CSF MTBR-tau markers in pathologically-confirmed cohort.** CSF MTBR-tau275/t-tau (A, C) and MTBR-tau282/t-tau (B, D) by pathological diagnoses (A, B) and clinical syndromes (C, D) are shown (total n=112). The box plots show the minimum, 25 percentile, median, 75 percentile, and maximum. Dotted lines show cutoff of 0.00563 and 0.01220, respectively for CSF MTBR-tau275/t-tau and MTBR-

tau282/t-tau. (E) Schematic of relationship between clinical syndrome and pathological diagnoses in FTLD. Red and black lines show CSF MTBR-tau biomarkers positive and negative, respectively. Biomarker positivity was determined by the median of each disease group. NC: normal control, FTLD-TDP: frontotemporal lobar degeneration with TAR DNA-binding protein, PiD: Pick's disease, AGD: argyrophilic grain disease, PSP: progressive supranuclear palsy, CBD: corticobasal degeneration, FTLD-MAPT: frontotemporal lobar degeneration with *MAPT* mutations (P301L, S305I), bvFTD: behavioral variant of frontotemporal dementia, CBS: corticobasal syndrome, nfvPPA: nonfluent variant primary progressive aphasia, PAGF: pure akinesia with gait freezing, PSP-RS: Progressive supranuclear palsy with Richardson's Syndrome, CN: cognitively normal.