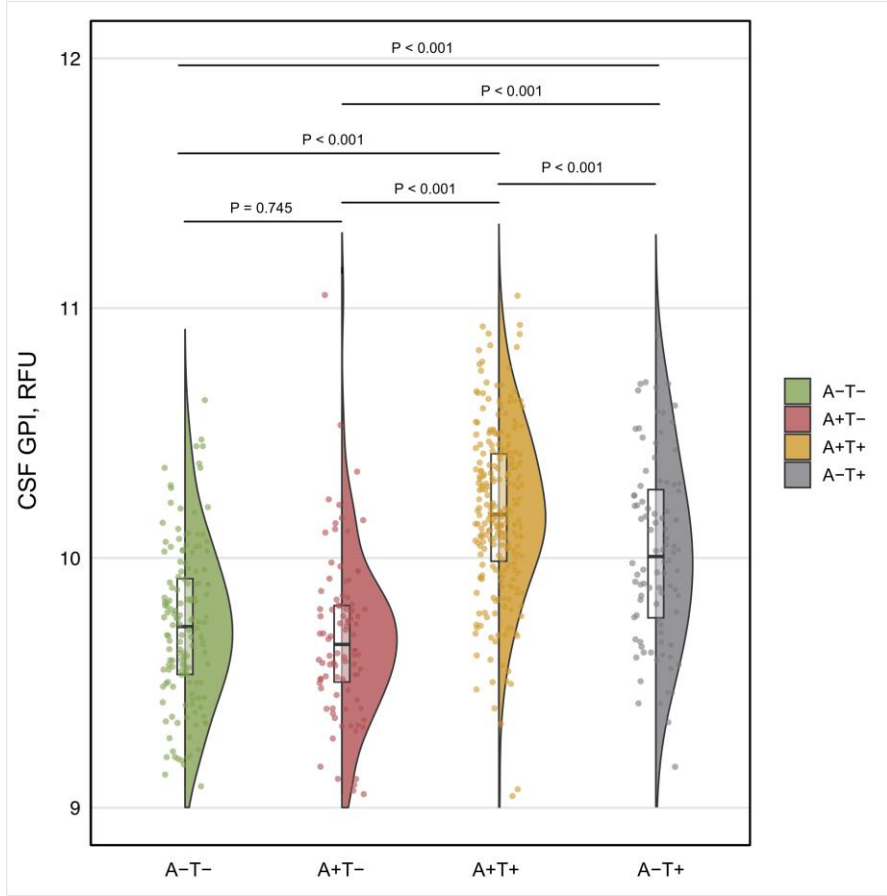
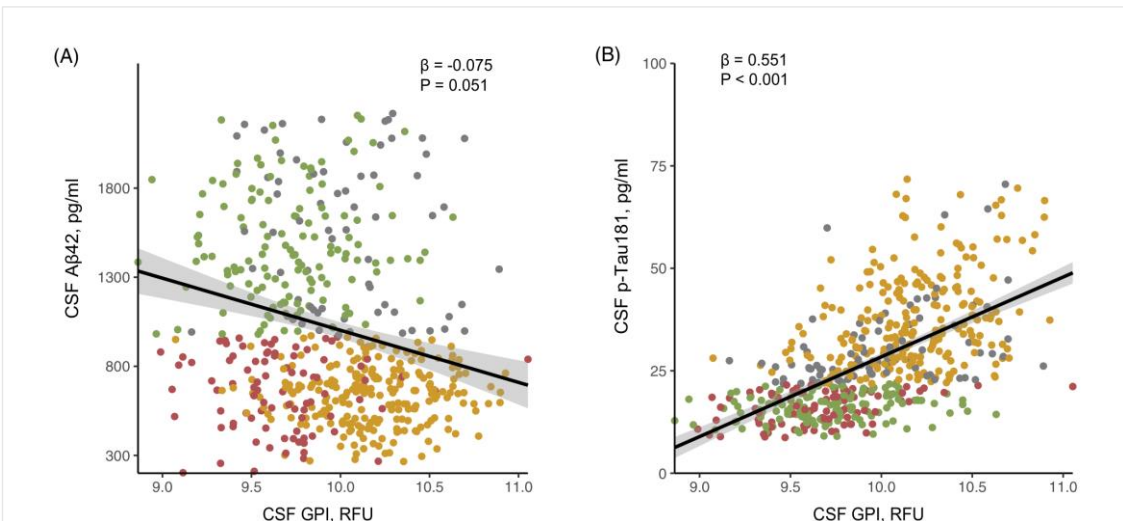
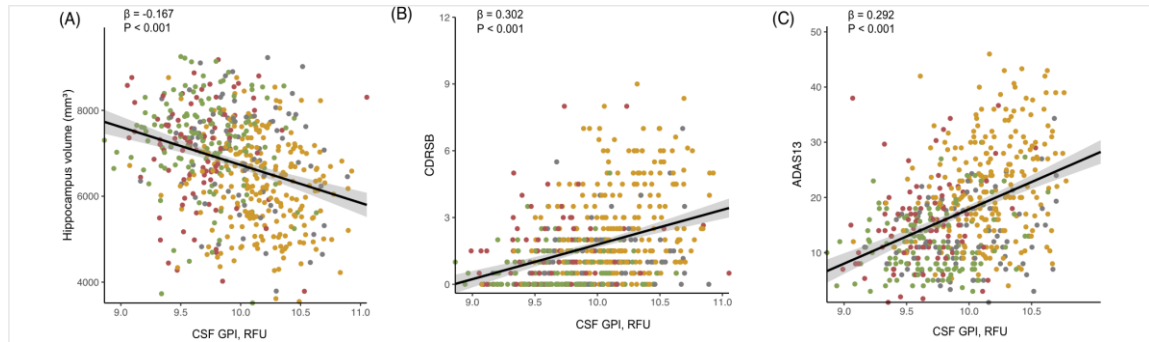
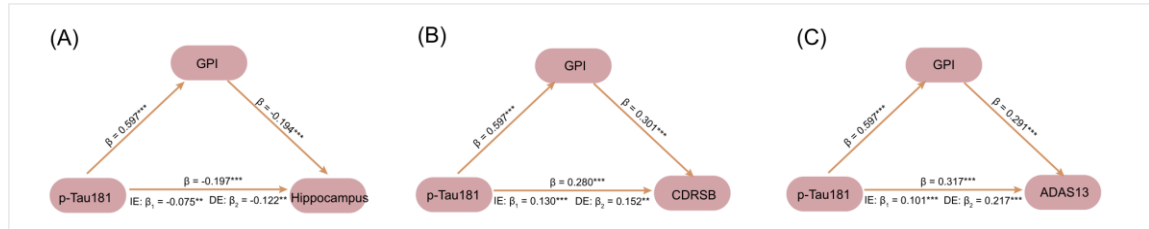
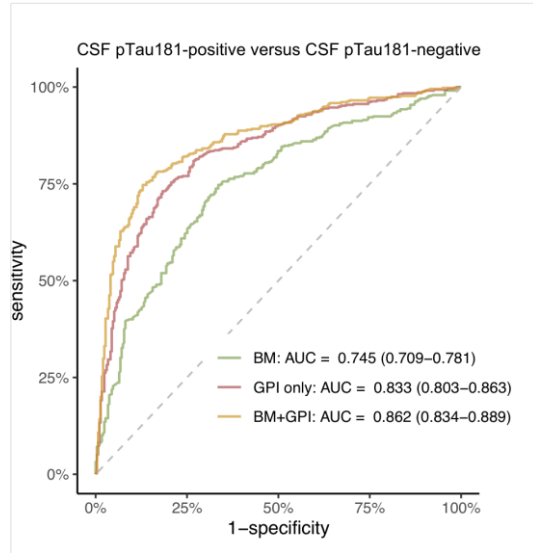


Cerebrospinal Fluid Glucose-6-Phosphate Isomerase as a Tau-Related Biomarker in Alzheimer's Disease

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Alzheimer's disease · GPI · Tau · Biomarker · Hippocampus · Magnetic resonance imaging · Cerebrospinal fluid · Diagnose

INTRODUCTION	METHODS	RESULTS	RESULTS	CONCLUSIONS
Skeletal diseases are epidemiologically and biologically linked to Alzheimer's disease (AD), but the molecular mechanisms connecting skeletal-related metabolic proteins with AD pathology remain unclear. Glucose-6-phosphate isomerase (GPI) is a key glycolytic enzyme involved in skeletal disorders and inflammatory processes. However, whether cerebrospinal fluid (CSF) GPI is associated with AD pathological progression, especially tau-related changes, has not been systematically investigated in humans. This study aimed to evaluate whether CSF GPI is associated with amyloid and tau pathology, neurodegeneration, cognitive impairment, and whether it may serve as a tau-related biomarker in AD.	This cross-sectional study included 601 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI), including cognitively normal individuals and participants with cognitive impairment. CSF GPI levels were measured using the SomaScan 7K proteomic platform. Core AD biomarkers included CSF Aβ42 and p-Tau181. Participants were classified into A/T pathological groups according to established CSF cutoffs. MRI-based neurodegeneration was assessed using hippocampal volume and other AD-related brain regions. Cognitive performance was evaluated using CDRSB and ADAS13. Linear regression models were used to examine associations between CSF GPI and AD biomarkers, neurodegeneration, and cognition. Mediation analyses tested whether CSF GPI mediated the relationship between tau pathology and downstream neurodegeneration or cognitive impairment. Diagnostic performance was assessed using ROC analysis. Findings were validated in two independent external cohorts, including an autopsy-confirmed Braak staging cohort and a cross-platform proteomics cohort.	1) GPI is elevated in tau-positive groups  2) GPI tracks tau, not amyloid  • p-tau181 association: $\beta=0.551$, FDR $P<0.001$. • Aβ42 association: $\beta=-0.075$, FDR $P=0.051$.	3) GPI relates to atrophy and cognition  Higher GPI associated with lower hippocampal volume and worse CDRSB/ADAS13 scores. 4) Mediation + diagnostic utility   • GPI partially mediated p-tau181 effects on hippocampal volume and cognition. • GPI only: AUC=0.833 for p-tau181 status. • Baseline model + GPI: AUC=0.862. • GPI partially mediated p-tau181 effects on hippocampal volume and cognition. • GPI only: AUC=0.833 for p-tau181 status. • Baseline model + GPI: AUC=0.862.	In summary, our results demonstrate that CSF GPI is specifically linked to tau pathology independent of amyloid pathology and partially mediates the relationship between tau pathology and cognitive impairment. Given GPI's role as a glycolytic enzyme in skeletal disorders and our demonstration of its tau-specific association in AD, these findings suggest that GPI dysfunction may represent a shared pathophysiological mechanism linking skeletal conditions and AD through metabolic-tau pathways. Collectively, these results contribute to our understanding of AD pathogenesis and suggest that CSF GPI warrants further investigation as a potential secondary biomarker for AD. However, additional validation studies will be needed before considering its application in clinical diagnostic evaluation or monitoring therapeutic responses. CONTACT Yuhan Chen sdr_cyh@163.com Sha Li, PhD lisha@hebm.u.edu.cn Department of Human Anatomy, Neuroscience Research Center, Hebei Medical University, Shijiazhuang, China  ALZHEIMER'S ASSOCIATION AAIC>26