Novel Glial Biomarkers Are Associated With Amyloid Pathology

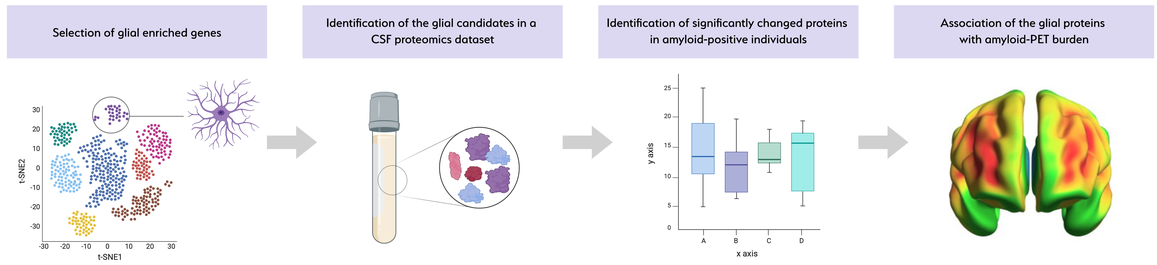
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Introduction

Glial cells play important roles in the pathophysiology of neurodegenerative diseases, including Alzheimer's disease (AD).[1-3] Glial dysfunction is thought to contribute to disease progression, but few known cerebrospinal fluid (CSF) biomarkers effectively capture these changes.[4,5] Identifying novel glial-derived CSF biomarkers may improve our understanding of AD pathology and aid in disease monitoring.

Methods



Results

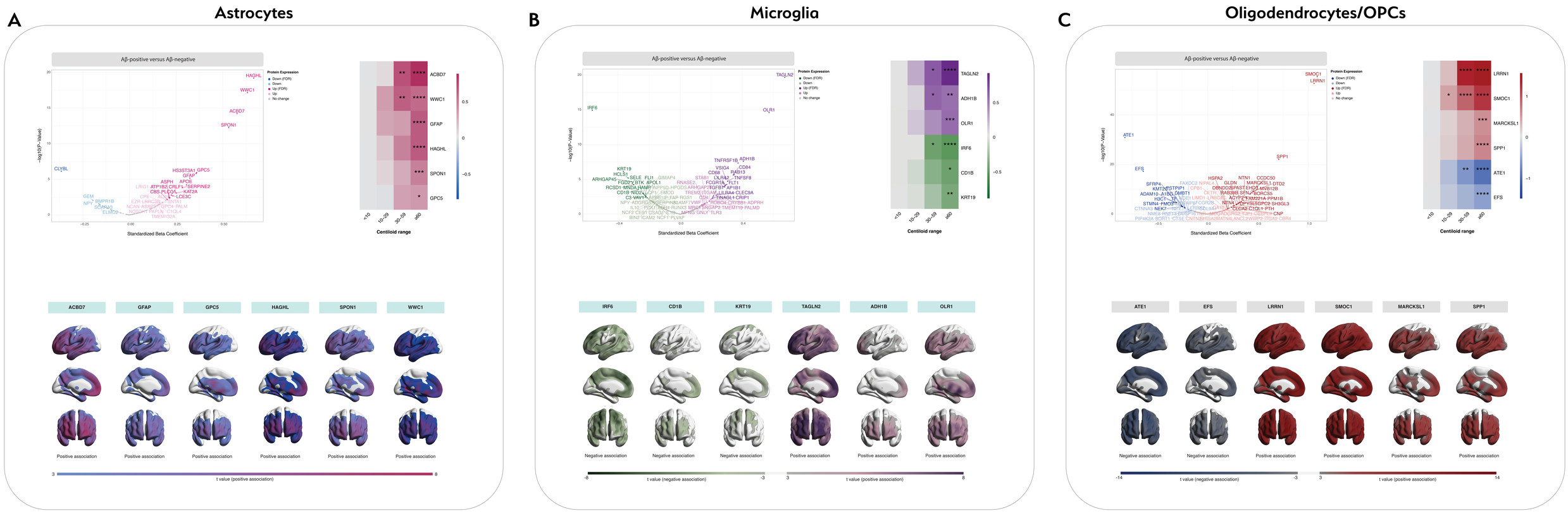


Figure 1. Astrocyte-, microglia-, and oligodendrocyte/OPC-related CSF protein alterations across Alzheimer's disease progression in the ADNI cohort. Panels show (A) astrocyte-related, (B) microglia-related, and (C) oligodendrocyte/OPC analyses. Within each panel, the upper left shows a volcano plot of differential CSF protein expression (z-scored $\log_{10}$ relative fluorescence units; RFU) in the SomaLogic proteomic dataset comparing Aβ+ (n = 340) and Aβ− (n = 388) individuals. Volcano plots display standardized beta coefficients on the x-axis and $-\log_{10}$(p-values) on the y-axis. Linear regression models were adjusted for age and sex, and false discovery rate (FDR) correction was applied for multiple comparisons. The upper right shows a heatmap of the top six z-standardized $\log_{10}$ protein levels among proteins significantly differentially expressed in the volcano plot analysis (nominal or FDR-adjusted $p < 0.05$) across Centiloid (CL) ranges derived from [18F]florbetaben PET (n = 461). The x-axis displays CL groups defined as <10, 10–29, 30–59, and ≥60 CL. Protein levels were z-standardized relative to the <10 CL group. Group differences were assessed using linear regression models adjusted for age and sex, followed by Tukey's post hoc test, with FDR correction for multiple comparisons. Heatmap colors represent standardized effect sizes (blue = lower, red = higher relative to the <10 CL group). Significance levels are indicated as follows: $p < 0.05$, $p < 0.01$, $p < 0.001$, and $p < 0.0001$. The bottom shows voxelwise associations between [18F]florbetapir PET and CSF protein levels for proteins identified as significant in the heatmap analysis ($t > 3.1$, $p < 0.05$; n = 461). Imaging models were adjusted for age and sex, and random field theory (RFT) was used to correct for multiple comparisons. Images are displayed on the ICBM152 3D template.

Conclusion

This study specifically targets candidates that are highly enriched in glial cells, of which 91 were altered in CSF with elevated cerebral amyloid burden. We also uncovered distinct glial proteins across amyloid pseudo-progression and their association with Aβ burden in the brain, highlighting potential glial biomarkers for disease progression.

References

1. Patani R, Hardingham GE, Liddelow SA. Functional roles of reactive astrocytes in neuroinflammation and neurodegeneration. Nat Rev Neurol. 2023.
2. Sasmita AO, Depp C, Nazarenko T, et al. Oligodendrocytes produce amyloid-β and contribute to plaque formation alongside neurons in Alzheimer's disease model mice. Nat Neurosci. 2024.
3. Blujdea ER, van Bokhoven P, Martino-Adami PV, et al. Microglia protein profiles in CSF across Alzheimer's disease clinical stages. Nat Aging. 2026.
4. Benedet AL, Milà-Alomà M, Vrillon A, et al. Differences Between Plasma and Cerebrospinal Fluid Glial Fibrillary Acidic Protein Levels Across the Alzheimer Disease Continuum. JAMA Neurol. 2021.
5. Zetterberg H, Bendlin BB. Biofluid biomarkers in Alzheimer's disease and other neurodegenerative dementias. Nature. 2026.

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