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BIOMARKERS (NON-NEUROIMAGING)

Proteogenomic Evaluation of Cerebrospinal Fluid in Alzheimer's Disease

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Abstract

Background: Alzheimer's disease (AD) is a complex disorder with a strong genetic component, yet many genetic risk factors remain unknown. Integrating genome-wide association studies (GWAS) and high-throughput proteomic platforms is a useful strategy to evaluate protein quantitative trait loci (pQTLs) and to detect candidate genes and pathways involved in AD. Due to the novelty of these techniques, the

identification of reliable protein measures through a comprehensive quality control is mandatory.

Method: We researched the cerebrospinal fluid (CSF) proteome using the SOMAscan 7k (7289 proteins), and the Olink Explore (2943 proteins) platform in the Ace Alzheimer Center Barcelona CSF Cohort. To assess reproducibility and reliability of proteomic measures, we analysed 1) intra-platform correlation of two independent SOMAscan assays using two aliquots of the same sample, and 2) inter-platform correlation between SOMAscan and Olink techniques. We also explored associations of highly reliable proteins with the AD Polygenic risk score (PRS) and the conversion to AD dementia. Additionally, we have performed an extensive pQTLs mapping of the SOMAscan platform and analysed pQTLs of significant proteins linked to disease progression.

Result: Our results revealed 2469 proteins with high intra-platform correlation (rho≥0.5), selected as candidates for further analysis. Moreover, over 600 proteins demonstrated strong inter-platform correlation, reinforcing their robustness. Extending our analysis to the entire CSF cohort (n=1322), we identified 85 proteins (Padj.<0.05) associated with the AD-PRS. Additionally, 93 significant proteins were linked with conversion to AD dementia. Strikingly, these conversion-associated proteins exhibited 89 genome-wide significant pQTLs in the genome, with more than 47% of the genetic signals localized within the APOE-rs429358 locus.

Conclusion: Our findings emphasize the importance of reliability assessment of highly multiplexed proteomic panels. Using robust measures, we identified significant proteins related to AD genetic risk and disease progression. These insights deepen the AD pathogenesis understanding, expand future research and therapeutic interventions.