bPRIDE

Towards plasma protein biomarkers for the differential diagnosis of dementia: a multi-center effort

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Aims, research questions and working hypothesis
Dementia places a substantial burden on society and can result from various neurodegenerative diseases like Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). Accurate differential diagnosis is challenging due to overlapping clinical symptoms. Blood-based biomarkers present a valuable, minimally invasive, and cost-effective option for diagnosis, enabling early disease detection and monitoring. Within the bPRIDE consortium, we aimed to 1) evaluate the differential diagnostic performance of known plasma biomarkers for AD across multiple international centers and to 2) identify novel plasma biomarkers for these purposes.

Means/methods implemented by the consortium
Plasma samples (n=1,298) were collected from six international centers of individuals along the clinical continuum of AD, DLB and FTD. The presence of amyloid pathology was determined by either PET or cerebrospinal fluid biomarkers. The concentrations of established AD plasma biomarkers (Aβ42, Aβ42/Aβ40, pTau181, GFAP and NfL) were measured using Single Molecule Array. The diagnostic performance of these biomarkers was assessed through multivariate modelling and ROC analyses. Additionally, the relative abundances of 1472 proteins were assessed through proximity extension assay (Olink proteomics). Novel biomarkers for AD staging and differential diagnosis between clinical groups were identified through differential expression analysis and LASSO regression modelling on these proteomics measurements.

What are the outcomes of the project?
Amongst the established biomarkers for AD, plasma Aβ42 and the Aβ42/pTau181 ratio demonstrated the strongest performance in distinguishing AD from DLB without amyloid co-pathology, as well as from FTD. Additionally, several novel biomarkers were identified for differentiating DLB from AD and for AD staging, leading to the design of a multi-marker panel consisting of 21 proteins for these purposes. A customized multiplex assay for the designed multi-marker protein panel is currently being developed, and will be validated with 1000 plasma samples of patients along the clinical continuum of AD, DLB and FTD.

Significance and impact of the work on the field
Plasma biomarkers are promising tools for early and specific diagnosis of neurodegenerative diseases. Indeed, they allow noninvasive, molecular profiling of patients, enabling personalized treatment planning as new therapies emerge. This work advances diagnostic accuracy through the identification of novel plasma biomarkers and the construction of robust multi-marker panels, promoting the clinical utility of plasma biomarkers in dementia care.

Next steps and future challenges
The dataset created by bPRIDE is a valuable resource for further research. Currently, we are using the bPRIDE dataset in research aimed at improving the diagnostic performance of AD plasma biomarkers by addressing inter-individual variability in biomarker levels. Specifically, our goal is to identify plasma markers that can adjust for this variability. In addition to supporting this research, the bpRIDE dataset also offers an opportunity for exploring other research questions and validating novel findings in different cohorts.