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BIOMARKERS

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BIOMARKERS (NON-NEUROIMAGING)

CSF proteome profiling reveals novel specific diagnostic biomarkers for Dementia with Lewy bodies

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Abstract

Background: Diagnosis of dementia with Lewy bodies (DLB) remains challenging and biomarkers discriminating DLB from Alzheimer's disease (AD) are highly needed. We aimed to establish the specific cerebrospinal fluid (CSF) proteomic changes that underlie DLB and to identify translatable diagnostic biomarkers.

Methods: Proximity extension-based multiplex immunoassays were used to measure 665 proteins in 534 CSF samples from patients with Dementia with Lewy bodies (n=109), AD-dementia (n=235) and cognitively-unimpaired controls (CON, n=190) from the Amsterdam Dementia cohort (ADC) and Penn University. An additional multi-center cohort (n=307) from ADC and SPIN was used for validation of custom assays. A positive/negative AD CSF profile supported the diagnosis of AD and CON respectively.

Results: Nested linear models identified 97 CSF proteins with altered abundance in DLB compared to controls ($p<0.05$). After comparison with the AD CSF proteome,

we observed that 52 of these proteins (54%) were especially associated to DLB (e.g. DDC, GH, FCER2, MMP1), while 15 proteins (16%) showed opposite changes to those detected in AD patients (CRH, MMP3). The protein with the highest fold-changed observed in DLB was L-amino acid decarboxylase (DDC; >1.5 fold-change vs.CN or AD; q<1E-16), an enzyme involved in dopamine biosynthesis. DDC could optimally discriminate DLB from controls and AD patients (AUC: 0.91 and 0.81 respectively). Using penalized generalized linear modelling we identified a panel of 7-CSF markers including DDC that could discriminate DLB from AD patients with high accuracy (AUC: 0.93, 95%CI: 0.86-0.98), which have been successfully translated into customized multiplex assays (correlations > 0.84 with discovery measurements).

Conclusions: We unveil CSF changes specifically related to DLB and identified a panel of 7-CSF markers associated to several aspects of DLB pathophysiology that enables discrimination of these dementia types with high accuracy. Multiplex custom assays containing these markers are currently being clinically validated in independent cohorts for their potential use in diagnostic settings or clinical trials.