Identification of NPTX2 as a Prognostic Biomarker of Alzheimer's Disease through a Longitudinal CSF Proteomics Study in ADNI Subjects

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INTRODUCTION

Many biomarkers have been identified which are relevant to studies of Alzheimer's disease, especially pertaining to the evolution of amyloid plaque, tau tangle pathology and loss of brain tissue. There remains, however, the need for additional biomarkers that reflect pathologic processes affecting neuronal function during pre-clinical and prodromal stages, to help accelerate drug development efforts.

Detailed clinical characterization of subjects and longitudinally collected samples in conjunction with employing a rigorous method of absolute quantification of analyte concentration using targeted mass spectrometry allowed us to estimate the shape of the mean within-subject trajectory of the concentration of five analytes in the subjects' CSF. By correlating these trajectories with the evolution of the subjects' clinical characteristics, we were able to assess the suitability of using the selected analytes as early prognostic biomarkers in patients meeting clinical criteria for MCI.

METHODS

A retrospective investigation of longitudinal changes in concentrations of five analytes (FABPH, CMGA, SCG2, VGH and NPTX2) was performed in CSF of ADNI subjects. The five analytes were selected based on evidence gathered from prior research including a cross-sectional proteomic study of CSF samples from the ADNI cohort published previously by our team (Spellman et al., 2015, https://doi.org/10.1002/prca.201400178)

Rates of longitudinal change in these candidate proteins were compared between:

a) Cognitively normal subjects (CN; n = 76) versus subjects with mild cognitive impairment (MCI; n = 111) at baseline;

b) Subjects categorized as p-Tau$_{181}$ / Aβ$_{1-42}$ ratio positive versus negative at baseline; and

c) 'Progressors', i.e., subjects who progressed from CN to MCI or MCI to Dementia within 4 years versus subjects categorized as 'non-progressors'.

Following a pre-specified analysis plan involving mixed-effects linear models adjusting for relevant covariates, the association between changes in each analyte's concentration and subjects' clinical progression was quantified.

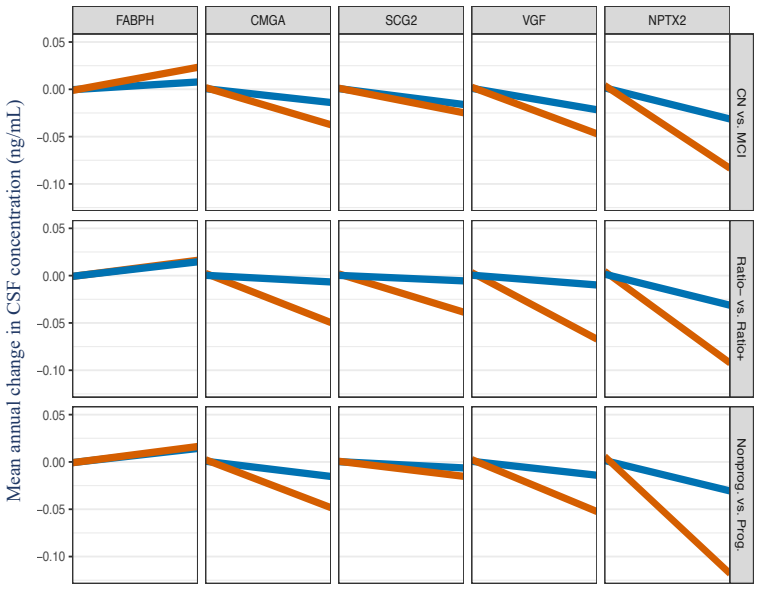
RESULTS

1. Differences in the rates of decline in NPTX2 concentration between subjects classified as CN and MCI as well as between p-Tau$_{181}$ / Aβ$_{1-42}$ ratio positive and negative subjects were highly significant ($p = 0.008$, $p < 0.0001$), suggesting a complex interaction between the rate of decline in subjects at various stages along the disease continuum.
2. Of the five analytes, only the rates of change in NPTX2 concentrations differed between progressors and non-progressors (mean difference: 0.08 ± 0.02 ng/mL/year; $p = 0.0004$).
3. Additional exploratory analyses indicated the presence of a correlation between NPTX2 rates of change and declining cognition measured by MMSE (coef. = 0.3, p = 0.02), and Adas-Cog 13 (coef. = -0.3, p = 0.01). This extends a cross-sectional similar finding in AD subjects. (Xiao et al, 2017, https://doi.org/10.7554/eLife.23798.001)

Demographic and clinical characteristics of study subjects

	Cog. normal (N = 76)	MCI (N = 111)	Total (N = 187)
Age (mean ± sd)	75.5 ± 5.5	71 ± 7.3	73 ± 6.9
Sex (% female)	49%	40%	43%
Education (years; mean ± sd)	16.1 ± 2.9	16.3 ± 2.7	16.2 ± 2.8
ApoE (% ε4 carriers)	22%	50%	39%
No. of visits (median, range)	3 (3–7)	3 (3–8)	3 (3–8)
Years of follow-up (median, range)	4.1 (3–10.2)	4 (2.8–10.1)	4 (2.8–10.2)
Progressors (%)	13%	26%	21%
p-Tau$_{181}$/Aβ$_{1-42}$ ratio (baseline mean ± sd)	0.026 ± 0.021	0.042 ± 0.039	0.036 ± 0.034
p-Tau$_{181}$/Aβ$_{1-42}$ ratio (% baseline positive)	32%	55%	46%
MMSE (mean ± sd)	29.3 ± 1.1	27.7 ± 1.8	28.4 ± 1.7
ADAS-cog (mean ± sd)	8.7 ± 4.5	15.4 ± 6.2	12.6 ± 6.5

Mean annual rates of change in the concentration of assayed analytes in the CSF



Mean and individual changes in the concentration of NPTX2