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CSF Biomarkers

Identifying amyloid pathology–related cerebrospinal fluid biomarkers for Alzheimer's disease in a multicohort study

Yuk Yee Leung[a], Jon B. Toledo[b], Alexey Nefedov[c], Robi Polikar[d], Nandini Raghavan[e], Sharon X. Xie[f], Michael Farnum[g], Tim Schultz[g], Young Baek[b], Vivianna M. Van Deerlin[b], William T. Hu[h], David M. Holtzman[i], Anne M. Fagan[j], Richard J. Perrin[k], Murray Grossman[l], Holly D. Soares[m], Mitchel A. Kling[n], Matthew Mailman[g], Steven E. Arnold[o], Vaibhav A. Narayan[g], Virginia M-Y. Lee[b], Leslie M. Shaw[b], David Baker[g], Gayle M. Wittenberg[g], John Q. Trojanowski[b,**], Li-San Wang[a,*], for the Alzheimer's Disease Neuroimaging Initiative

[a]*Department of Pathology & Laboratory Medicine, Institute on Aging, Institute for Biomedical Informatics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA*

[b]*Department of Pathology & Laboratory Medicine, Institute on Aging, Center for Neurodegenerative Disease Research, Philadelphia, PA, USA*

[c]*Department of Pathology & Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA*

[d]*Department of Electrical and Computer Engineering, Rowan University, Glassboro, NJ, USA*

[e]*Department of Quantitative Science, Janssen Research & Development, LLC, Titusville, NJ, USA*

[f]*Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA*

[g]*Department of Neuroscience, Janssen Research & Development, LLC, Titusville, NJ, USA*

[h]*Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA*

[i]*Department of Neurology, Knight Alzheimer's Disease Research Center, Hope Center for Neurodegenerative Disorders, Washington University, St Louis, MO, USA*

[j]*Department of Neurology, Knight Alzheimer's Disease Research Center, Hope Center for Neurodegenerative Disorders, Washington University, St Louis, MO, USA*

[k]*Department of Pathology and Immunology, Division of Neuropathology, Knight Alzheimer Disease Research Center, Hope Center for Neurological Disorders, Washington University, St Louis, MO, USA*

[l]*Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA*

[m]*Clinical Biomarkers, Bristol-Meyer Squibb, Hopewell, NJ, USA*

[n]*Behavioral Health Service, Philadelphia VA Medical Center, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*

[o]*Department of Neurology, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA*

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*Corresponding author. Tel.: +1-215-746-7015; Fax: +1-215-573-3111.

E-mail addresses: trojanow@mail.med.upenn.edu (J.Q.T.), lswang@mail.med.upenn.edu (L.-S.W.)

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Abstract

Introduction: The dynamic range of cerebrospinal fluid (CSF) amyloid β ($A\beta_{1–42}$) measurement does not parallel to cognitive changes in Alzheimer's disease (AD) and cognitively normal (CN) subjects across different studies. Therefore, identifying novel proteins to characterize symptomatic AD samples is important.

Methods: Proteins were profiled using a multianalyte platform by Rules Based Medicine (MAP-RBM). Due to underlying heterogeneity and unbalanced sample size, we combined subjects (344 AD and 325 CN) from three cohorts: Alzheimer's Disease Neuroimaging Initiative, Penn Center for Neurodegenerative Disease Research of the University of Pennsylvania, and Knight Alzheimer's Disease Research Center at Washington University in St. Louis. We focused on samples whose cognitive and amyloid status was consistent. We performed linear regression (accounted for age, gender, number of apolipoprotein E (*APOE*) e4 alleles, and cohort variable) to identify amyloid-related proteins for symptomatic AD subjects in this largest ever CSF–based MAP-RBM study. ANOVA and Tukey's test were used to evaluate if these proteins were related to cognitive impairment changes as measured by mini-mental state examination (MMSE).

Results: Seven proteins were significantly associated with $A\beta_{1–42}$ levels in the combined cohort (false discovery rate adjusted $P < .05$), of which lipoprotein a (Lp(a)), prolactin (PRL), resistin, and vascular endothelial growth factor (VEGF) have consistent direction of associations across every individual cohort. VEGF was strongly associated with MMSE scores, followed by pancreatic polypeptide and immunoglobulin A (IgA), suggesting they may be related to staging of AD.

Discussion: Lp(a), PRL, IgA, and tissue factor/thromboplastin have never been reported for AD diagnosis in previous individual CSF–based MAP-RBM studies. Although some of our reported analytes are related to AD pathophysiology, other's roles in symptomatic AD samples worth further explorations.

Keywords: Cerebrospinal fluid; Biomarkers; Alzheimer's disease; Cognitive impairment; Amyloid beta; Dementia

1. Introduction

Alzheimer's disease (AD) is pathologically characterized by the presence of extracellular amyloid plaques (APs) and intracellular hyperphosphorylated tau neurofibrillary tangles, which are known to be correlated with cerebrospinal fluid (CSF) levels of amyloid β ($A\beta_{1–42}$), total tau (t-tau), and phosphorylated tau ($p\text{-}tau_{181}$) [1,2]. The measurements of these proteins in the CSF using enzyme-linked immunosorbent assay (ELISA) and xMAP technology were able to distinguish most AD and cognitively normal (CN) subjects [3,4]. These CSF biomarkers are included in the revised version of the commonly used diagnosis criteria Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) in 2011 for supporting clinical diagnoses [5]. Analyses of CSF $A\beta_{1–42}$, t-tau, and $p\text{-}tau_{181}$ in a meta-analysis study (combining 11 different studies) were shown to accurately classify AD patients (area under the curve, 0.86) [6]. Nevertheless, CSF $A\beta_{1–42}$ reaches pathologic values and then plateau during the preclinical phase of the disease, when subjects still have normal cognition, and therefore show low correlation with cognitive symptoms [7]. Although CSF t-tau levels show a better correlation with cognition, there is a need for additional CSF biomarkers that track cognitive changes closely. Due to the heterogeneity of the disease populations, it is critical to validate identified biomarker candidates across different cohorts.

Recent studies have been conducted to identify and characterize other potential CSF biomarkers, as reviewed by Fagan and Perrin [8]. These include visinin-like protein-1 and chitinase 3-like 1 (cartilage glycoprotein-39; YKL-40) for which follow-up studies explored their roles in different disease populations [9–11]. However, disappointingly, most of the other candidate biomarkers have not been replicated to date. Comparing to $A\beta_{1–42}$ and t-tau, they possibly participate in different time frames in the AD spectrum [12,13]. Therefore, by combining cohorts comprised subjects with different levels of cognitive deficits, we postulate that the candidate biomarkers may better explain the disease progression in a heterogeneous population defined by cognitive measures such as mini-mental state examination (MMSE) as opposed to more global clinical status (AD vs. CN).

Multiplex methods can identify CSF biomarkers altered in AD and have utility as potential diagnostic and disease staging tools, and for nominating novel drug targets and tracking treatment responses for investigational interventions. Hu et al. [14] previously conducted a study on subjects from the University of Pennsylvania (UPenn) using the Human DiscoveryMAP panel from Rules Based Medicine (MAP-RBM), where they identified CSF biomarkers (including thirteen analytes from the MAP-RBM) for distinguishing pathologically confirmed AD from CN subjects. Another study involved subjects recruited at Knight Alzheimer's Disease Research Center at Washington University