Novel Strategies for Blood-based Biomarkers for AD: Role of Genetic Variation in a Multivariate Framework

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Research Abstract

? DESCRIPTION (provided by applicant): Without any successful drug trials for Alzheimer's disease (AD) treatment and proven efficient therapies for AD, early detection of AD in asymptomatic or prodromal stages is critically important in order to increase chances of reducing irreversible brain damages, slowing down disease progression, and producing better results in any intervention trials. Several biomarkers from MRI, PET, CSF, and peripheral blood show their potential as diagnostic, prognostic, or therapeutic response biomarkers. Among them, blood-based biomarkers, especially proteomic analytes from peripheral blood have great potential as AD screening tools due to its minimal invasiveness and easy access of collection method and would have an extraordinary impact on research and eventually clinical care to facilitate the investigation of early intervention. During the last couple of years, many studies have been performed to investigate the direct relationship between a set of measured plasma (serum) proteomics analyte levels and a set of AD relevant phenotypes using various assay technologies. Due to several technical challenges related to sample collection, storage and assay, previous studies couldn't fully investigate the potential of plasma proteomics data, resulting in relatively weak replications. Beyond these technical issues, previous studies to date overlooked two very important factors: influence of genetic variations associated with each protein analyte and correlational structure of multi-analyte proteomic data. Recently we have shown that genetic variation substantially influences plasma proteomic analyte levels independent of disease status. Therefore, in assessing the diagnostic and prognostic significance of proteomic data, gene variants should be taken into account. Another potential reason of weak replication could be relative weak diagnostic power of individual analytes because the majority of investigation focused on the effect of each measured protein analyte level on a set of given phenotype. In many cases, multianalyte molecular biomarkers are correlated with one another and most of studies using plasma proteomics analytes did not consider correlational structure among analytes when assessing their diagnostic potential. Although the diagnostic power of individual analyte can be weak, multivariate approaches to identify a set of biologically meaningful ensembles of analytes may better elucidate diagnostic and prognostic power of plasma proteomic signature. In this proposed study, we will address these two knowledge gaps in assessing potential of plasma proteomic analytes through a multivariate approach by applying advanced analytic methods including multi-dimensional data reduction, gene pathway-enrichment analysis, imaging genetics, and supervised and unsupervised learning. Results of this project could have a transformative impact on identification and evaluation strategies of proteomic analytes as diagnostic, prognostic, or therapeutic response biomarkers and proposed advanced analytical strategies can be applied to fluid-based multi-analyte data for various neurodegenerative disorders in addition to AD.

Further information available at:

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