A BLOOD-BASED SIGNATURE OF CEREBRAL SPINAL FLUID $A_{\beta_{1-42}}$ STATUS

Benjamin Goudey, Christine Schieber, Bowen J. Fung, Noel G. Faux

1IBM Research-Australia, Southbank, Australia; 2School of Psychological Sciences, University of Melbourne, Parkville, Australia; 3Florey Institute of Neuroscience and Mental Health, Parkville, Australia. Contact e-mail: bgoudey@au1.ibm.com

Background: Early detection of molecular changes in Alzheimer’s disease is likely to play a key role in the success of interventions aimed at slowing down rates of cognitive decline. Recent evidence indicates that of the two established methods for measuring amyloid, decreases in cerebral spinal fluid (CSF) amyloid ($A$) levels may be an earlier indicator of Alzheimer’s disease risk than measures of amyloid obtained from Positron Emission Topography (PET). However, CSF collection is highly invasive and expensive. In contrast, blood collection is routinely performed, minimally invasive and cheap. In this work, we develop a blood-based signature that can provide a cheap and minimally invasive estimation of an individual’s CSF amyloid status.

Methods: We make use of 57 cognitively normal (CN) and 186 mild cognitively impaired (MCI) individuals from the ADNI dataset, who have measures of CSF $A$, 149 protein (P) and 140 metabolites (M) levels measured in blood and age and APOE4 status (B) at baseline. A random forest approach in 10 repetitions of 10-fold cross validation is used to get an unbiased estimate of the model performance. An independent 210 MCI individuals without CSF measures are used to validate our model’s performance by examining the difference in rates of conversion to AD between the predicted abnormal/normal CSF $A$ strata.

Results: We show that a Random Forest model derived from age, APOE and proteins levels (BP) can accurately predict pre-clinical subjects as having abnormal (low) CSF $A$ levels indicative of AD risk (Fig 1: 0.80 AUC, 0.69 sensitivity, and 0.75 specificity). Only 3 analytes are required to achieve similar high levels of accuracy (BP5, 0.78 AUC). Furthermore, we show across an independent validation cohort that individuals with predicted abnormal CSF $A$ levels transitioned to an AD diagnosis over 120 months significantly faster than those predicted with normal CSF $A$ levels (Fig 2: P < 2.5’10$^{-6}$).

Conclusions: This is the first study to show that a plasma protein signature, together with age and APOE4 genotype, can predict CSF $A$ status, the earliest risk indicator for AD, with high accuracy, further highlighting the potential for developing a blood-based signature for improved AD screening.

CELL-FREE, SINGLE-STRANDED DNA CONCENTRATION IN CSF AS BIOMARKER TO DIAGNOSE ALZHEIMER’S DISEASE STATUS

Josue D. Gonzalez Murcia, Lyndsay Staley, Meganne Ferrel, Henrik Zetterberg, John Kauwe

1Brigham Young University, Provo, UT, USA; 2Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden. Contact e-mail: josuegon.mur@gmail.com

Background: Many researchers have discovered that cerebrospinal fluid (CSF) contains potential biomarkers for neurological and psychiatric diseases such as AD that may facilitate monitoring of amyloid beta (AB-42) deposition in the brain. The purpose of this study is to evaluate if quantitative endophenotype cell free single stranded DNA (cfssDNA) concentration is correlated with the diagnosis of development of AD.

Methods: We examined three independent cohorts two from Sweden and one from Italy. The first cohort 32 CSF non-demented samples and 27 CSF samples of AD cases from Sweden. The second cohort 13 CSF non-demented control samples and 21 CSF samples of AD cases from Italy. The third cohort 27 CSF non-demented samples and 21 CSF samples of AD cases from Sweden. We extracted single stranded DNA from all CSF samples and measured using Qubit assay technology. During this process we screened for dsDNA, RNA, and ssDNA. We then proceeded to analyze measurements using a T test pair...