Biomarkers (DPUK 1000)
Work Package 6

Objective(s):

To conduct high dimensionality molecular analyses to identify biomarkers for early detection of Alzheimer's disease and related phenotypes.

These objectives to be met through:

1. Construction of three DPUK cohorts, stratified by risk, for biomarker studies to include: 1) cohorts stratified by risk factors and early disease phenotypes; 2) an amyloid cohort, 3) rare genetic variants; complementing work in WP2 (informatics), WP5 (familial risk), and WP14 (Biostatistics).
2. Establishing a DPUK biomarker bio-resource.
3. Data generation.

Overview Summary:

By applying both proteome wide differential analysis and protein co-expression network analysis, our findings offer new insights into changes in individual proteins and protein networks linked to AD pathology markers as well as the ATN framework in poorly understood preclinical stages of AD. Those nominated hub proteins are tractable targets for further mechanistic studies of AD pathology. It also suggests that the relationships between plasma proteins and "N" are dependent on the choice of neurodegeneration marker, indicating that the ATN variants are not interchangeable.

Executive Summary:

Alzheimer's disease (AD) is characterised by the presence of β-amyloid (Aβ) containing plaques and neurofibrillary tangles composed of modified tau protein together with the progressive loss of synapses and neurons. Currently, the best characterized methods for measuring amyloid or tau pathology are positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) measurement. Blood-based biomarkers show promise as a less invasive and potentially cost-effective option for the detection, classification and monitoring of AD pathology. So the objective of this project is to conduct high dimensionality molecular analyses to identify biomarkers for early detection of Alzheimer's disease and related phenotypes.

Summary of Outputs: (as per Researchfish categories)

Publications:

- Shi L. et al, 2018, J Alzheimer's Dis, 62, 1181 - 1198

In which we summarised the biomarkers that we have identified and replicated in Alzheimer's disease (AD) patients during the last two decades. Furthermore, we stated the challenges and future direction of AD biomarker development.

- Shi L. et al, 2019 Alzheimer's Dement. 15(11):1478-1488.

In which we found a panel of proteins predict amyloid status with high performance in both discovery and validation cohort. Furthermore, we found there is causal relationship between amyloid and tau, while the reverse relationship between tau and amyloid was not found.

- Shi L. et al, 2020, J Alzheimer's Dis, 77(3):1353-1368.

In which we firstly nominated candidate blood biomarkers in vitro through Dickkopf-1 overexpression, we then validated these nominated biomarkers in two large independent cohort to explore their associations with Alzheimer's pathology.

- Shi L. et al, 2021 Alzheimer's Dement (in press)

In which we sought to discover and replicate plasma proteomic biomarkers relating to Alzheimer's disease (AD) including both the "ATN" (Amyloid/Tau/Neurodegeneration) diagnostic framework and clinical diagnosis.

Collaborations & Partnerships

None

Further Funding

None

Next Destinations

None

Engagement Activities

- S Lovestone - Speaker at launch of UK Dementia Platform talk on the NIHR-MRC Dementia Deep and Frequent Phenotyping Feasibility Study 2015

Influence of policy, practice, patients & the public

None

Research Tools & Methods

- Discovery study protocol
- Processes in place for targeted biomarker analysis
- Processes in place for untargeted biomarker analysis (SomaLogic)

Research Databases & Models

None

Intellectual property & licencing

None

Medical products, interventions & clinical trials

None

Artistic & creative products

None

Software & technical products

None

Spin outs

None

Awards & recognition

None

Other outputs & knowledge/future steps

None

Use of facilities & resources

None

Other:

None

Most successful outcome and what it means for future dementia research:

We have identified a panel of proteins predict amyloid status with high performance. These proteins could help select the right participants for the right trials, thus having high clinical value. Furthermore, we have found there is causal relationship between amyloid and tau, confirming the central role of amyloid in Alzheimer's.

Lessons learned:
First, we learned how to deal with the contract, especially when multiple collaborations are involved. In order to move projects forward, good communication with all collaborators is critical. Second, we learned the importance of having back up plans. For example, in this project, we have not developed the MSD assays for target analyses because of technique issue of the platform. We therefore measured more plasma samples using Somalogic assay.
Date of Report:
02/03/2021