Alzheimer’s disease specific alternative splicing in the brain

EBI PI: Irene Papatheodorou  
BRC PI: Steven Kiddle

The EMBL-EBI,  
Wellcome Trust Genome Campus,  
Hinxton, Cambridge,  
CB10 1SD  
irenep@ebi.ac.uk

MRC Biostatistics Unit,  
University of Cambridge,  
Forvie site, Robinson Way,  
Cambridge, CB2 0SR  
steven.kiddle@mrc-bsu.cam.ac.uk

https://www.ebi.ac.uk/about/people/irene-papatheodorou  
https://www.mrc-bsu.cam.ac.uk/people/in-alphabetical-order/h-to-m/steven-kiddle/

Aim: Characterise alternative splicing in the brain of Alzheimer's disease patients, and relate to Alzheimer’s disease pathology using functional genomics

Background: Alzheimer's disease (AD) is a fatal disease which in the UK alone directly affects 820,000 people, costing the UK economy £23 billion pounds, more than cancer and heart disease combined. All current treatments for Alzheimer's disease (AD) only provide temporary relief from symptoms, despite many attempts to develop a cure. The core pathology of AD involves the proteins amyloid beta and tau, produced from the genes APP and MAPT respectively. However, our lack of effective treatments shows that there is a lot we don’t yet understand about the disease.

Alternative splicing is a widespread mechanism by which a single gene can be translated into multiple related proteins, for example by adding or subtracting specific protein domains. It’s relevance to AD is clear, both APP and MAPT, as well as the major genetic risk factor for late onset AD, APOE, are known to have disease specific alternative splicing variants [1]. In this project we aim to fully characterise alternative splicing in the AD brain, and then to gain mechanistic understanding in order to highlight potential drug targets and biomarkers.

Main datasets

Brain RNA-seq data from the Accelerating Medicines Partnership - AD [2] on a total of 1,341 individuals.

Research proposal

Aim 1: Identification of any splicing events linked to Alzheimer's disease

The first aim would be to identify splicing events associated with Alzheimer’s disease across different RNA-Seq data sets from human brain tissue. This task would involve extracting publicly available Alzheimer’s Disease data sets, running the splicing pipelines available through the Gene Expression Team at EMBL-EBI [3] and performing suitable meta-analyses to identify links to AD. Candidate genes, such as MAPT, APP, APOE, PSEN1 and PSEN2 [2], would be the first point of investigation that would then be followed up by looking in an unbiased manner across all splicing events across the genome.
Aim 2: Functional characterisation of prioritised targets

Splice variants could be associated with AD via different mechanisms, uncovering these, could shed light on disease progression and may help identify biomarkers, suitable for testing. We would employ functional genomics approaches to try and understand the function of AD associated splice variants, in terms of their effect on the biological activity of the proteins. On that end, we would also interrogate available CSF mass spectroscopy data sets from EMBL-EBI’s PRIDE database and would investigate co-expression networks as well as biological pathways in order to explore further downstream effects that could contribute to the disease phenotype.

Aim 3: Explore specificity of identified splice variants in other diseases/cell types

An additional aim of this project would be to test the specificity of the AD associated splice variants against a wider spectrum of neurodegenerative disorders. Finally, using currently available and upcoming single cell data sets from healthy human brain samples in the context of initiatives such as the Allen Brain Atlas and Human Cell Atlas, we will investigate whether any of these targets show specific expression in different cell types.

Partners and training opportunities

The candidate will be embedded in a strong multidisciplinary team. The Papatheodorou group at the EBI will provide access to cutting-edge bulk and single cell RNA-seq data and processing pipelines. Steven Kiddle is an MRC Career Development Award fellow with a decade of experience with gene expression data, and 6 years of experience in AD biomarker statistics. The fellow will be fully embedded in both groups and able to strongly develop both the computational and statistical aspects needed for modern post-genomic research.

References