The StrataStem Manchester AD Cohort: Sporadic Alzheimer's Disease is Associated with Ciliopathic SNPs

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Overview

Dementia is the leading cause of death and one of the main causes of disability later in life, ahead of cancer, cardiovascular disease and stroke. Alzheimer's disease (AD) is the most common form of dementia, accounting for 60% of all dementia diagnoses. Despite new AD therapeutics becoming available, there remains a lack of understanding of the molecular and cellular mechanisms associated with the early stages of the disease.

Introduction

In this study, we have derived iPSCs from 200 patients diagnosed with sporadic Alzheimer's disease and assessed neuronal cultures derived from these cells to determine pathogenic Aß42 peptide secretion and performed RNA-seq analysis to identify pathways associated with early stages of the disease and SNPs that may aid diagnosis.

Methods

HRA approved study REC 19/NW/0656; IRAS 268793. PBMCs were reprogrammed to iPSCs using the CytoTune™-iPS 2.0 Sendai Reprogramming Kit (ThermoFisher, UK). iPSCs were differentiated to cortical neurons in poly-L-ornithine/laminin coated 6-well plates cultured with Neurobasal media, B27, glutamine, NEAA for 30d at 37°C/5% CO_2. Aβ42 and Aβ40 in culture medium was assessed at d30 of differentiation using ELISA analysis (Invitrogen, UK). RNA-seq was performed by Leeds University NGS facility.

Results

60% of AD patient neurons were found to secrete elevated levels of pathogenic Aß42 peptide within the culture medium compared to healthy controls. 1,112 differentially expressed transcripts were identified in AD patients (897 upregulated; 215 downregulated), with significant enrichment for genes associated with cilia. 90 ciliopathic SNPs in 31 genes have been identified in the StrataStem Manchester AD cohort, with Aβ42 secretion levels positively correlating with the number of SNPs (r2 = 0.746).

Conclusion

Our results may suggest a conserved mechanism of disease (either specific ciliopathy or widespread cytoskeletal dysfunction manifesting as ciliopathy) occurs in sporadic AD via mutations in a range of

genes associated with normal ciliary function. Our work demonstrates the potential for a panel of iPSC AD models for use in understanding the mechanisms associated with very early stages of the disease as well their use in therapeutics development.

For information and access to the StrataStem Manchester Cohort iPSC lines, please contact our partner, Axol Bisocience, at operations@axolbio.com