Functional Genetic Analysis: Mechanisms of Dementia in People with Down syndrome

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Research question and background

Down syndrome (DS) is caused by the presence of an extra copy of chromosome 21. Most people with DS develop early-onset Alzheimer's-type dementia, with most people in their 40s with DS have Alzheimer's disease (AD) pathology, such as amyloid plaques and neurofibrillary tangles.

A tetranucleotide repeat polymorphism has been found in intron 7 of the amyloid precursor protein (APP), which affects the age of onset of dementia in DS. The tau gene, which produces the protein which forms neurofibrillary tangles, has also been associated with dementia in DS.

The aim of this study is to determine how polymorphisms affecting Alzheimer's-type dementia in people with Down syndrome (DS) alter Alzheimer's pathology in the brain. We will examine the impact of polymorphisms in APP, tau and other genes involved in the development of AD pathology upon age at onset of dementia, severity, and levels of Aβ and tau.

Methods and tissues used

This study focuses on the entorhinal cortex and cortical areas BA9 and BA20; regions associated with pathological changes in AD.

DNA and RNA have been prepared using the commercially available kits. Protein has been extracted for Western blotting and ELISAs

All samples have been genotyped for the APP intron 7 polymorphism and tau haplotype, and a preliminary genome-wide association study has been carried out.

Clusterin levels have been measured by Western blotting. Aβ1-40, Aβ1-42, tau and phospho-tau concentrations were measured using commercially available ELISAs. Further Western blotting for APP, DYRK1A and actin levels is being carried out. APP and tau RNA levels will be measured using Taqman gene expression assays.

Results and conclusion

We have found that genes which are risk factors for AD in the general population may also affect the onset of dementia in people with DS. Levels of Aβ1-40, Aβ1-42, tau and phospho-tauS396 were correlated with age in the three brain regions analysed.