Molecular Investigations of Frontotemporal Lobar Degeneration

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Title of project or programme

Molecular Investigations of Frontotemporal Lobar Degeneration

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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Source of funding information

Medical Research Council

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Total duration of award in months

60

The project/programme is most relevant to

- Alzheimer’s disease and other dementias

Keywords

Research abstract in English

Neurodegenerative diseases of our progressively more aged society are becoming an increasing social and economic burden. Frontotemporal lobar degeneration (FTLD) is the second most common form of dementia after Alzheimer’s disease. Up to 40% of patients have a family history of this

disease indicating a large genetic component to its aetiology. Approximately 5% of cases are caused by mutations in the MAPT gene encoding the microtubule associated protein, tau. Patients with MAPT mutations display a prominent tau-based neuropathology at autopsy. Around a further 5% of cases are caused by null-mutations of the pleiotropic growth factor, progranulin (PGRN) and the neuropathological features of these comprise of neuronal inclusions containing ubiquitinated TDP-43 protein. Until the discovery of mutations in PGRN very little was known about the function of this protein in the CNS. Preliminary data: Using linkage disequilibrium mapping of the recently reported FTLD ch9p linkage region, we identified genetic association of UBAP1 (Ubiquitin Associated Protein 1) within our FTLD cohort (214 patients, 286 controls; MAPT and PGRN mutation -ve). Analysis revealed SNPs/haplotypes were consistently associated with a maximum OR of 1.71 (95% CI 1.20-2.44, P=0.003). Crucially, we successfully replicated this association in a Dutch FTLD cohort (230 FTLD cases, 484 controls) with a maximum haplotype association of OR 1.39 (95% CI 1.02-1.89, P= 0.033). This argues that UBAP1 is a novel risk factor for FTLD and likely the gene responsible for linkage to this region. Using antibodies to UBAP1 we have shown this protein co-localises with tau in the neuronal perikaryon in FTLD. Furthermore, UBAP1 interacts with progranulin demonstrated by immunoprecipitation. These data suggest UBAP1 maybe important in regulating the amounts of these proteins via the ubiquitin proteosome system. I propose to identify and functionally characterise the genetic variants driving the UBAP1 association and characterise UBAP1 in human brain and existing mouse models of FTLD. In addition, we have shown that PGRN treatment of primary neurons and glia activates ERK. I propose to investigate the downstream effects of this signalling pathway using microarray analysis and to identify PGRN’s receptor using affinity chromatography. Finally, I will investigate the role of UBAP1 in regulating levels of tau and PGRN using siRNA knockdown and expression of known UBAP1 mutations. This work could provide a paradigm shift in our understanding of the aberrant biological pathways controlling proteins important in FTLD and other neurodegenerative diseases. This work could highlight potential therapeutic targets.

Lay Summary