Project Title: Analysis of the frontotemporal dementia - motor neuron disease gene TBK1	**Code: CCS10**

Host School / Institute: Central Clinical School/ Brain and Mind Centre

Address: Brain and Mind Centre, Building M02-K, Level 3 Lab

Certificates & Clearances required: Yes *Vaccination Certificate

Information on how to obtain certificates, where necessary, will be given to successful applicants.

Primary Supervisor: Dr Carol Dobson-Stone

Phone: 02 9351 0822

Email: carol.dobson-stone@sydney.edu.au

Co-Supervisor/team: Carol Dobson-Stone is a Senior Research Fellow at the Brain and Mind Centre and will act as primary supervisor for the project. Assistance will also be provided by postdoctoral research associate Dr Lisa Oyston, and research assistants Ms Marianne Hallupp and Ms Lauren Fitzpatrick will be on hand to provide support in the lab.

Project Type: Laboratory based; Data Analysis

Project Category: Molecular biology; Genetics

Skills / Attributes of a successful student: This project would suit an organised student who is able to work carefully and independently and has an eye for detail. Prior knowledge of molecular biology and/or genetics is preferred.

Project Keywords: Dementia; Amyotrophic lateral sclerosis; Cell culture

Project Description: Frontotemporal dementia (FTD), a common cause of early-onset dementia, is characterised by behavioural and/or speech changes followed by progressive cognitive deficits arising from degeneration of nerve cells (neurons). About 15% of FTD patients also develop motor neuron disease (MND), a rapidly progressive disorder starting with muscle weakness and leading to paralysis. There are no effective cures for FTD or MND and both conditions are fatal. Our understanding of these diseases has been greatly enhanced by identifying the genes and pathways that underlie the neurodegenerative process. Some FTD and MND patients have mutations in a gene called TBK1. Although some TBK1 mutations cause a complete loss of gene product and are therefore predicted to cause disease, most TBK1 variants lead only to a small alteration of the protein structure. For these ‘missense’ variants it is not clear whether they are truly pathogenic or just benign variants unrelated to disease.

The aim of this project is to identify the effect of these missense variants on TBK1 function. This will be achieved by making DNA constructs with TBK1 variants by site-directed mutagenesis, and assessing how cell signalling is affected when these DNA constructs are introduced, using molecular biology and cell culture techniques. Identifying which TBK1 variants are pathogenic will enable diagnosis and genetic counselling for patients who harbour these variants. It will also identify which regions of the TBK1 protein are important for its function, which is critical information needed for designing new therapies for these disorders.

Acquired Skills And Techniques: Experimental design, Molecular biology techniques (e.g., PCR, Sanger sequencing, bacterial transformation, mammalian cell transfection).