Project title: Human Endogenous Retroviral Involvement in Sporadic Amyotrophic Lateral Sclerosis (sALS)

Studentship Code: FST9

Amyotrophic Lateral Sclerosis (ALS), also known as motor neuron disease, is a fatal neurologic disorder of unknown cause, characterised by the degeneration of motor neurons and resulting in progressive paralysis and death from respiratory failure, usually within 5 years from onset. Viral involvement in the etiology of sporadic ALS has been suspected, with most focus on retroviruses as a cause of motor neuron disease in humans (eg; Human T Lymphotropic virus (HTLV) type1; and HIV which causes ALS like syndromes). In particular, Human Endogenous Retroviruses (HERVs) have been implicated in ALS. These are remnants of ancient germ line infections with exogenous retroviruses, that have been genetically fixed and vertically transmitted millions of years ago, and constitute 8% of the human genome.

In a previous study, we found evidence for retroviral involvement in ALS by demonstrating cell-free reverse transcriptase (RT) activity (a generic screening method for retroviruses) in the serum of 50% of patients with sALS compared with 7% in controls. Based on these findings, the primary aim of this PhD proposal, is to clarify the role of HERVs in sALS, and in doing so to identify potential new avenues for disease diagnosis and potentially treatment which is lacking to date.

Initial screening will focus on the HERVK retroviruses, due to the presence of complete open reading frames and the ability to form virus like particles (VLPs), and their known association with inflammatory disorders of the central nervous system, including multiple sclerosis and schizophrenia.

Expression of HERVK gene transcripts (gag, pol, env) will be measured in post-mortem frozen brain tissue samples from sALS patients along with controls that are matched for age, sex, and post-mortem interval, utilising SYBR Green quantitative real-time PCR (qPCR) methodology and input RNA that is of high integrity.

Samples identified as positive by qPCR, will be followed up using next generation sequencing (NGS) using MiSeq platform in collaboration with colleagues at King’s College London and UCLH to detect putative minority variants (≤1-5%) in HERVK gene transcripts encoding viral capsid, reverse transcriptase and envelope proteins. In addition, microarray technology will be utilised to screen for all major HERVs and human exogenous retroviruses, comparing ALS versus non-ALS brain tissue at biopsy.

The student will learn a range of techniques including molecular biology, NGS and cell culture and will take part in the University Graduate School and Faculty Doctoral Research Development Programme, and will also gain invaluable transferable skills (scientific writing, presentation skills). The student will be part of the Cell Communication Research Group and will be encouraged to join the Amyotrophic Lateral Sclerosis Association (ALSA) and the Motor Neuron Disease Association (MNDA) and present their research findings at scientific meetings.

Related publications

Contact
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For details of how to apply
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