Project Details	
Project Code	MRCNMH26Ex Lunnon
Title	Investigating the role microRNAs play in the pathophysiology of Huntington's disease and whether they could be targeted therapeutically
Research Theme	NMH
Project Type	Wet lab
Summary	Huntington's disease (HD) is a neurodegenerative disorder caused by a CAG expansion in the HTT gene, with age of onset influenced by additional genetic and environmental factors. This PhD project will investigate the role of microRNAs—key post-transcriptional regulators—in mediating this variability. Using cutting-edge short- and long-read sequencing technologies in post-mortem HD brain tissue, the project will identify microRNA signatures associated with age of onset and pathology, and relate these to transcriptional changes and genetics. Functional validation will be performed in an iPSC model of HTT expansion. The student will receive interdisciplinary training in genomics, neuroscience, stem cell models and bioinformatics.
Description	Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterised by progressive motor dysfunction, psychiatric symptoms and cognitive decline. Neurodegeneration is initially most pronounced in the striatum, but also extends to cortical regions as the disease progresses, leading to neuronal dysfunction and widespread brain atrophy. Symptoms usually start in mid-life and progress over 10-30 years, culminating in dementia and premature death. There is no disease-modifying treatment. HD is caused by a CAG trinucleotide repeat expansion in the HTT gene. Alleles with at least 36 CAGs cause HD, with ≥40 repeats being fully penetrant. Longer repeats are associated with earlier onset of symptoms, with length accounting for ~60% of the variance seen. Much of the remaining variance is heritable suggesting genetic or shared environmental factors can modulate disease progression and may offer novel therapeutic targets. Recent genome-wide association studies (GWAS) have identified several genes that influence the onset and progression of HD. Many of these genes encode DNA repair factors that modulate the mosaic expansion of the CAG repeat in somatic cells. Larger expansions are seen in the striatal neurons that are most susceptible in HD, particularly in those with earlier onset disease. Epigenetic mechanisms such as DNA methylation (DNAm), histone modifications, and non-coding RNAs play a central role in mediating gene–environment interactions and are increasingly recognised as important contributors to neurodegeneration. Our research group is internationally recognised for leading large-scale epigenome-wide association studies (EWAS) in neurodegenerative disease brain tissue. We have identified robust DNAm signatures in Alzheimer's disease (AD) and Lewy body diseases (LBDs), and recently conducted the first EWAS of DNAm in HD striatum, highlighting novel loci. This work has led to new MRC funding to conduct a larger, integrated analysis of DNAm, genetic variation, histone modifications, and transcriptional diversity in HD.

	While DNAm is the most widely studied epigenetic mark in neurodegeneration, we are increasingly interested in the role of non-coding RNAs—particularly microRNAs, which regulate gene expression post-transcriptionally by promoting mRNA degradation or inhibiting translation. MicroRNAs regulate ~60% of mammalian protein-coding genes and are implicated in neurodegenerative processes. We recently completed large-scale small RNA-sequencing studies in AD and LBD, identifying reproducible disease signatures associated with downstream gene and protein expression changes. Despite the emerging interest in RNA-based therapeutics—including a microRNA approach to lower HTT in HD clinical trials (Uniqure: AMT-130)—no comprehensive analysis of miRNA expression in HD brain tissue has been performed. Existing studies have relied on candidate gene approaches or small sample sizes, limiting their utility. We hypothesise that alterations in microRNA expression in HD brain contribute to pathogenesis and inter-individual variability in age of onset, regulating transcriptional networks and mediating genetic and environmental influences. This interdisciplinary PhD project will address this hypothesis through the following aims: 1. microRNA profiling in HD brain Using small RNA-sequencing, the student will perform a systematic assessment of miRNA expression in HD striatal tissue, leveraging a well-characterised post-mortem cohort collected through our MRC funding. Analyses will identify miRNA signatures associated with disease status, CAG repeat length, and neuropathological stage. 2. Integration with transcriptomic and genetic data The student will apply long-read sequencing to quantify full-length transcripts of miRNA target genes and known HD modifiers, enabling the identification of novel splice isoforms and differential expression patterns. Using advanced bioinformatics, they will integrate GWAS and long-read DNA sequencing data (quantifying CAG repeat length) that we have generated in the same samples to map microRNA-regulated networks relevant to disease onset and progression and explore how these relate to genetic variation. 3. Functional validation in iPSC models Key findings will be validated using an induced pluripotent stem cell (iPSC)-derived HD neuronal model. They will manipulate microRNA levels using siRNA or miRNA mimics and assess downstream effects on target gene and protein expression (qRT-PCR, Western blotting). Functional readouts will include somatic CAG repeat expansion, neuronal morphology and survival, mitochondrial function, and HTT expression and aggregation. This project offers outstanding interdisciplinary training in epigenomics, transcriptomics, neuroscience, and bioinformatics. The student will develop expertise in sequencing technologies, stem cell modelling, molecular assays and computational biology. The project builds on complementary strengths across institutions: Exeter's expertise in microRNA profiling and bioinformatics, and Cardiff's in iPSC modelling and HD functional genomics. A key component of the studentship is a secondment at Maastricht University's Systems Biology Group, where

	the student will receive training in advanced network and computational analyses. The project is structured around defined aims but offers substantial scope for the student to steer the direction of their work. Depending on their interests and initial findings, the student could choose to explore other non-coding RNA species (measured in the small-RNA sequencing), integrate other omic measures in the same samples (e.g. DNAm), or compare with our AD/LBD data. This project addresses a major gap in our understanding of microRNAs in HD, with potential to uncover novel disease mechanisms and therapeutic targets.
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