Project Details	
Project Code	NMH27Br Hodge
Title	Using human genomics, AI and fly disease modelling to study the relationship between sleep and Alzheimer's disease
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	With ageing your 24-hour clock (circadian rhythms) and sleep get weaker. These symptoms are more pronounced in Alzheimer's with poor rhythms and sleep accelerating dementia. But how? Important answers lie within in our genes. You will learn the latest molecular analysis tools and AI to search human genomic data to identify genetic changes regulating circadian rhythms and sleep and occurring in ageing and Alzheimer's. To test your predictions, you will be taught how to make the equivalent genetic changes in the rapidly ageing fruit fly measuring if they cause the predicted changes in circadian rhythms, sleep, ageing, memory and neurodegeneration.
Description	Background Our 24hour body clock or circadian rhythms controls sleep-wake cycles timing. We helped show rhythms become weaker and sleep fragmented in old age (https://circadiageing.org.uk). In Alzheimer's disease (AD) these symptoms become more pronounced with poor sleep accelerating dementia pathology, with collaborators trialling sleep enhancement to slow dementia (https://www.bristol.ac.uk/news/2026/january/165-million-to-investigate-neurodegenerative-diseases.html). But why do some individuals sleep well and others not, likewise, why do some people get AD whilst others not. You will join our team looking at differences in our genomes to find the answers addressing the: Key research question: How do clock and sleep genes affect ageing and AD? Project Aim: To understand how differences in genomes cause changes in individual's circadian rhythms and sleep contributing to ageing and AD. Objectives: 1: Identify genetic changes associated with ageing, circadian rhythms, sleep and AD. You will learn from Prof Michael Weedon (Exeter University) to identify variants/mutations that influence sleep and circadian traits/phenotypes and define their causal links with ageing and AD. We have already identified 100's of common variants affecting sleep and circadian measures (https://www.nature.com/articles/s41467-018-08259-7; https://www.nature.com/articles/s41467-019-09576-1) and are using large-scale whole genome sequencing to identify rare high impact variants influencing sleep (https://pubmed.ncbi.nlm.nih.gov/36137075/) You will access circadian and sleep measures from >1million individuals in diverse cohorts who have been whole genome sequenced allowing testing of variants/mutations associated with the traits/phenotypes. Likewise, you will look at the large amount of publicly available 'omic data for ageing and AD cohorts to identify variants associated with circadian traits/phenotypes taking advantage of circadian transcriptomics database and tools e.g. www.bodyclocks.org and

	https://github.com/ranafi/CYCLOPS. We also have multi-omic data on local human brain samples that Dr Rosie Bamford (ECR) will lead on. 2: Use AI to help predict their relationship, directionality and effect To look for circadian and sleep variants associated with ageing and AD in >1million individuals 3.2 billion nucleotide genomes you will need big data and AI tools. You will learn from Dr Qiang Liu (Bristol University) to apply state-of-the-art AI (deep and machine learning) and bioinformatic techniques to gain a deeper understanding of how genetic variants confer risk to ageing and AD (https://pubmed.ncbi.nlm.nih.gov/39775791/), and to develop effective treatments (https://link.springer.com/article/10.1186/s12916-022-02250-2, https://pubmed.ncbi.nlm.nih.gov/41779422/). You will benefit from the research expertise, resources, training and ECR funding opportunities of https://www.ukfunctionalgenomics.com, and learn to use tools like AlphaGenome (https://www.nature.com/articles/s41586-025-10014-0), https://www.ensembl.org/ and https://platform.opentargets.org to predict functional consequences of variants/mutations and what is known about the gene, its expression and reagents in humans and model species. Also its potential as a drug target and candidates to modify/correct mutant functions. 3: Use Drosophila to test the functional consequences of the genetic changes on ageing, circadian rhythms, sleep and AD But how do you test the functional consequence of a gene variant associated with ageing, circadian, sleep and AD? In addition to the bioinformatic tools above and being taught to perform Mendelian randomisation https://pubmed.ncbi.nlm.nih.gov/34426474/. You will be supervised by Dr James Hodge (Bristol University), to use the platforms above, https://alice.nrihub.org, https://marrvel.org and https://fgr.hms.harvard.edu/diopt-dist to identify the equivalent genes and variants in the fly genome. ~80% of genes that cause human disease are found in Drosophila, with publicly available mutations in each gene https://flybase.org, a whole brain connectome (https://flywire.ai) and projects making publicly available humanized flies expressing human disease-causing genes and variants (https://www.yamamotoflylab.org/alzheimersdisease). You will be taught how to functionally characterize the role of a gene variant in ageing, circadian, sleep and AD, by testing flies with the equivalent gene mutated or flies expressing the human disease-causing gene (e.g. Tau or amyloid) or causally testing the gene variants/risk factors you identify (https://pubmed.ncbi.nlm.nih.gov/35569721/). Flies are not a protected species, have a 10-day generation time and 2-month lifespan. You will use publicly available fly mutants and humanized flies of the gene variants you identified, if necessary, you will use CRISPR genome editing to make the conserved change identified in the fly. You will learn to functionally screen your different fly variants for circadian rhythms, molecular clock rhythms, sleep, longevity/ageing, memory, neurodegeneration and enhancement/suppression of human AD-associated Tau, amyloid and ApoE4 phenotypes. Given time you will test genetic and pharmacological intervention e.g. from in silico modelling predicted to treat the gene variant's AD-like phenotypes. We have track record with working with Pharma testing novel dementia drugs in our fly

	AD models (https://pubmed.ncbi.nlm.nih.gov/35928283/), translating to rodent models (https://circadiageing.org.uk) and by collaboration to humans (https://www.circadianmentalhealth.org). Student ownership Will be encouraged throughout, we have an excellent track record in ECR training, you will be empowered with the skills allowing you to choose the approaches, cohorts, traits and 'omic databases. Likewise, you will have the opportunity to explore the different AI, bioinformatic and data platforms to interrogate data. You will choose which and how many gene variants you test in flies, and with which assays. You will be encouraged to present your work at conferences, write your own papers and apply for fellowships/ECR grants.
Can be completed part time?	Yes
Supervisory Team	
Lead Supervisor	
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