Project Details	
Project Code	MRCNMH24Ca Escott-Price
Title	Untangling neurodegeneration and ageing components of neuroinflammatory disorders
Research Theme	Neuroscience & Mental Health
Summary	Numerous genome-wide association studies (GWAS) show a strong, but poorly understood neuroinflammatory component to most neurological diseases. This project will leverage such GWAS data from several neurological and inflammatory conditions to determine the relationships between immune system genes and underlying neurological pathologies and in addition to understanding the genetic influence of aging-dependent inflammatory changes
Description	A major factor why we do not have effective drugs for neurodegenerative diseases is because these diseases are multifactorial and commonly not one pure disease. We hypothesise there are genetic subtypes of neurodegenerative disorders, and so the mechanisms and course of neurodegeneration can differ even if the end stage of these looks the same. Because of this heterogeneity the diagnosis is also confounded and this why clinical trials have not been successful. Untangling this heterogeneity by considering the influence of pleiotropic components within the human population is key to making a step-change breakthrough in neuroinflammatory disease. The immune components of most neurological diseases are not well understood, despite more than a decade of GWAS. Most neurological diseases have a strong neuroinflammatory component, including AD, PD, LBD, ALS, FTD etc. Our supervisory team is in the unique position of having access to GWAS data and pathology samples from all these neurological conditions, including those based on neuropathological diagnosis. The overarching goal for this project is to leverage this access to determine the relationships between the genetics of the immune system and underlying neuropathologies, including understanding the genetic influence of aging-dependent inflammatory changes. We will achieve this goal with this project through combined interrogation of the latest and largest GWAS of AD, PD, ALS, DLB, Aging, COVID-19, diabetes, asthma, and arthritis (accessible to Escott-Price and/or in public repositories). Analysing all these datasets together increases the power of the genetic analysis and will give novel and broader more generalisable insights into the common human genetic variation associated with inflammatory components. Genetic correlation between studies may in part be explained by a phenomenon, known as pleiotropy, which occurs when a genetic locus affects more than one trait. Since neurodegenerative conditions are highly comorbid, the joint analysis of related phenotypes has the potential to uncover additional associations, when instead considering one disease at a time dilutes the effect of some true genetic contributions, and where many useful samples showing comorbidities are excluded. Understanding the molecular mechanisms underlying pleiotropy is vital for understanding shared pathways of neurodegenerative disorders, particularly how different inflammatory challenges interact to alter risk and age of onset. Our project has the potential to identify loci relevant to the pathology of several disorders and thus more attractive from a drug targeting

	perspective. The aim of this project is to identify pleotropic loci between the inflammatory diseases in four ways: 1) investigate and apply the appropriate methodology (depending on genetic disease architecture, disease prevalence and cross-disorder correlations) to identify novel pleotropic candidate loci 2) use established cell biology approaches we deployed (with cell biology work at UCL, Dr Salih) for AD genetics by investigating of the mechanisms of action of pleiotropic loci with CRISPR or siRNA-modification of induced pluripotent stem cell (iPSC) differentiated to microglia and activated with different disease and immune stimulators. The student will then analyse how introducing knockout, knockdown or knock-in of the identified genes/variants affect cellular function using gene expression/ protein levels of markers of microglial function 3) use Genomic Structural equation modelling approach to derive novel GWAS summary statistics reflecting the shared genetic component between the neuroinflammatory disorders and unique component for each disorder. These summary statistics will be used to generate polygenic risk scores and investigated for predicting neuroinflammatory disorders in the UK Biobank (N~500,000) 4) run transcriptome-wise analyses to gain biological mechanisms of the disease specific and shared components.
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