Project Details	
Project Code	MRCNMH25Ca Szomolay
Title	Biomarker discovery of inflammatory pathways linked to mood and autoimmune disorders
Research Theme	Neuroscience & Mental Health
Summary	Mood disorders (MDs), e.g. depression, affect over one billion people worldwide. MDs show a bidirectional relationship with systemic inflammation, a key component in the pathophysiology of autoimmune disorders (ADs), e.g. rheumatoid arthritis. This exciting project will integrate genetic and metabolomics data from UK biobank to identify and experimentally validate novel biomarkers. Results will be utilised in developing new diagnostic tools for MD-AD comorbidity.
Description	**Background:** Mood disorders (MDs), such as depression and anxiety, are among the most pressing health problems worldwide, with over one billion people living with the condition. Studies have shown that there is a bidirectional relationship between MDs and systemic inflammation, which is a key component in the pathophysiology of autoimmune disorders (ADs), such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD) or systemic lupus erythematosus (SLE). It is now well established that aberrant production of cytokines characterises both MDs and ADs. For example, pro-inflammatory cytokines, such as TNF, IL-1, IL-6, and anti-inflammatory cytokines, such as IL-10, are produced by inflamed synovial tissues in RA. Similarly, the most studies cytokines in the context of psychoneuroimmunology are IL-6, TNF, IL-1, IFNs and IL-10. Proinflammatory cytokines regulate tryptophan metabolism by stimulating the enzyme indoleamine 2,3-dioxygenase (IDO). Tryptophan is involved in several physiological processes, and also acts as a precursor to the functional molecules, such as serotonin and melatonin in the brain. **Research question:** The reason for the development of autoimmune comorbidities in MDs remains unknown. Similarly, it is not understood why patients with ADs have some of the highest rates with MDs. This project will identify genetic variants (GVs) that associate with changes in the homeostasis of key metabolites by taking a metabolite genome-wise association approach (mGWAS) using data from UK Biobank. Moreover, the functional effect of shared causal genes between MDs and ADs, identified by the mGWAS analysis, on MD-related biological pathways (e.g. the kynurenine pathway of tryptophan metabolism) will be experimentally characterised. **Specific objectives:** (1) To identify novel GVs and loci shared between MDs and ADs using publicly available GWAS summary data. Bioinformatics analysis will utilise METAL, FUMA, SNP2GENE pipeline, STRING and cytoHubba. (2) To unify known and novel GVs from (1) and metabolomic traits in UK Biobank for mGWAS analysis in MDs comorbid with ADs. Statistical analysis will be carried out using PLINK, SNPTEST and LocusZoom. The combination of genotyping and metabolomic characterisation will be a step forward for determining epigenetic modifications in the prevention, diagnosis and treatment of complex diseases.

	(3) To identify and investigate the pleiotropic effects of the identified GVs on the disease-related metabolites from (2) in the context of their biochemical pathways. We will use cross-trait LD score regression (LDSC) for estimating genetic correlations using GWAS summary statistics, Local Analysis of [co]Variant Association (LAVA) and Association Analysis Based on Subsets (ASSET). (4) Using identified genetic and metabolomic determinants from (2), to estimate the potential causal effect on MDs comorbid with ADs by performing Mendelian randomization analyses in R. (5) Experimental characterisation of the functional effect of shared causal genes from (3) on MDrelated pathways. Techniques will include metabolomics, immunodetection assays and RNAseq. Impact: The identified biological pathways and associated molecules will facilitate future drug repositioning studies by matching drugs to biological pathways. Drug repositioning shortens the time and cost needed as compared to the traditional de novo approach. **Ownership:** The student will be supported by a multi-disciplinary supervisory team in every aspect of dry and wet lab work and will be encouraged to take a proactive approach, for example, by proposing achievable objectives or new research methods. The student will be first author on published work.
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