Project Details	
Project Code	MRCPHS24Br Min
Title	Harnessing the genetics of DNA methylation to understand context-specific gene regulation in disease
Research Theme	Population Health Sciences
Summary	Many disease risk factors have genetic and environmental influences. DNA methylation is also influenced by genetic and environmental factors and is a molecular mediator of gene regulation. DNA methylation can be used to understand how cells respond to environmental factors and how this influence can vary by genotype. This studentship will apply state-of-the-art genetic epidemiological approaches to identify genotype environmental interactions with DNA methylation.
Description	Background Genome wide association studies (GWAS) have discovered many genetic associations for traits and diseases. However, most GWAS signals reside in non-coding regions (outside genes), and it is likely that GWAS variants confer their effects through modulating regulatory mechanism. DNA methylation (DNAm) plays a central role in gene regulation and genetic variants associated with DNAm (methylation quantitative trait loci) have been used to provide a candidate mechanism underlying GWAS associations. However so far only a small proportion of GWA signals have been causally linked to mQTLs. One explanation for this could be that many of these mQTLs are cell type or tissue specific. For example most mQTL studies have identified mQTLs in blood. However, blood has a variety of cell-types which may obscure cell-type specific DNAm differences. In addition to tissue or cell type as a context, many other contexts can also have an influence. These environmental effects may operate through genotype-environmental interactions but evidence for these interactions is scarce. For example, sex, age or smoking habits may change your DNAm levels and induce interactions between genetics and DNAm(1). These context-specific interactions may induce the development of disease in individuals with a genetic predisposition. Similarly, the immune response occurring after infection can lead to gene environmental interactions associated with immune response diseases. However, the effect of context-specific mQTLs on disease is unknown. This PhD project offers an opportunity to address these knowledge gaps using large-scale DNAm and genetic datasets by collaborating with academic centres that participate in the Genetics of DNA Methylation Consortium. This studentship will provide cross-disciplinary training in state-of-the-art epigenetic, genetic and causal inference analyses. Aims and objectives: The aim is to get a better understanding of context-specific gene regulation and to identify causal influences between context-specific mQTLs and disease. The following are examples of specific research questions that the student may wish to address as part of their PhD. The student and supervisors will use the prep period to tailor and finalize research plans to reflect the student's interests. 1. Identify genetic factors for cell-type interacting DNA methylation variation 2. Identify genetic factors for sex, age and smoking dependent DNA methylation variation 3. Identify genetic factors for BMI and chronic inflammation dependent DNA methylation variation 4. Estimate infection status (for example cytomegalovirus infection) from DNA methylation and identify infection dependent DNA

	methylation variation 5. Identify causal associations between context-dependent mQTLs and health outcomes Methods The student will analyse genetic and DNAm data on cohorts that participate in the Genetics of DNA methylation Consortium (GoDMC; http://www.godmc.org.uk/). The student will identify context-specific mQTLs by modelling genotype environmental interactions where cell type, smoking, sex or BMI and can be taken as a proxy for the environment. GoDMC promotes a federated analysis protocol which means that the PhD student has an excellent platform to develop analysis skills for genetic and DNAm analysis and develop his/her own research questions. The student will apply Mendelian randomization analysis to identify novel causal factors influencing chronic diseases(2). Mendelian Randomization is a genetic epidemiological approach that uses genetic variants as proxies to interrogate potential causal links between exposure (eg cell counts) and outcome (disease). 1. Bergstedt J et al. The immune factors driving DNA methylation variation in human blood. Nat Commun. 2022;13(1):5895. 2. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet. 2014;23(R1):R89-98.
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