Project Details	
Project Code	MRCPHS26Br Min
Title	Exploring the epigenetic links between genes, environment and health
Research Theme	PHS
Project Type	Dry lab
Summary	How do cells respond to environmental exposures? How do these exposures interact with genetic factors to influence disease risk? This PhD project investigates the interplay between genetics, environmental exposures, and epigenetics with a focus on DNA methylation as a key mechanism of gene regulation. You will: • Apply genetic epidemiology and population health data science approaches on large epidemiological datasets • Identify gene-environment interactions that influence DNA methylation patterns • Explore how these interactions contribute to disease risk with Mendelian randomization Apply now to join an international research team and uncover biological mechanisms that link environmental factors to disease risk.
Description	**Background** Genome wide association studies (GWAS) have uncovered thousands of genetic associations linked to health outcomes. Yet, identifying the underlying mechanism linking an associated genetic variant with a health outcome is still a major challenge. One reason could be that these genetic variants exert their influence by modulating regulatory mechanisms. Molecular traits such as DNA methylation (DNAm), gene expression and protein levels have increasingly been used to provide insights on the gene regulatory mechanism of these GWAS variants. DNAm is a fundamental epigenetic modification process by which methyl groups are added to DNA molecules. This process is essential for regulating gene expression, maintaining cell identity, and responding to environmental factors. DNAm arrays have enabled measurement of hundreds of thousands DNAm sites across the genome in epidemiological datasets. DNAm variation among individuals can be influenced by various factors, including lifestyle factors, environmental exposures, and genetic factors. Studies have identified genetic variants associated with DNAm variation (mQTL: methylation quantitative trait loci) by combining genome-wide genotype information with DNAm sites across many healthy participants. We published a large mQTL study in >27,750 human blood samples from 36 European cohorts, where we found that 45% of DNAm sites had a genetic basis. Using statistical approaches that combine mQTL and GWAS data, we estimated causal relationships between DNAm levels and complex traits (1). Consistent with previous studies, we found that most disease-associated variants did not exhibit causal effects on DNAm sites, and conversely, most mQTLs did not have causal effects on disease risk (2). One possible explanation for these findings is that the link between DNAm and disease risk might depend on environmental factors. For example, most studies have identified mQTLs in blood as DNAm measurements in individual cell-types is expensive and laborious. However, blood comprises multiple cell-types, where each cell-type can

	exhibit a distinct DNAm pattern. Therefore, studying DNAm changes in blood may obscure cell-type specific DNAm differences (3). Computational approaches have shown that mQTLs that are specific to certain cell-types can be inferred from blood. This is achieved by estimating the proportions of the relevant cell-types in blood and then testing for interactions with genotype. This is similar as in gene-environment interaction models. The contribution of these cell-type mQTLs and other context-specific mQTLs to health outcomes is still lacking. We now need to generate catalogs of mQTLs that are dependent on environmental factors such as cell-type and study their influences on health outcomes. 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 (GoDMC, http://www.godmc.org.uk/). This studentship will provide cross-disciplinary training in state-of-the-art epigenetic, genetic and causal inference and population health data science 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. In the example below we use cell-type as environmental factor (or context), but the student may wish to choose a different environmental factor. 1. Identify genetic factors for cell-type interacting DNAm variation in blood 2. Identify causal associations between cell-type specific mQTLs and health outcomes 3. Validate genetic and causal associations in cell-type specific datasets Methods The student will analyse genetic and DNAm data on cohorts that participate in the Genetics of DNA Methylation Consortium. The student will identify cell-type specific mQTLs by modelling genotype environmental interactions where cell-type can be taken as a proxy for the environment. GoDMC promotes a federated analysis protocol (https://github.com/genetics-of-dna-methylation-consortium/godmc_phase2/wiki) where scripts developed by the student will be shared with contributing cohorts. This 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. To identify whether DNAm changes are causes or consequences of the health outcome, the student will apply Mendelian randomization (MR) analysis (4). 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). The student will validate the cell-type interacting mQTLs in DNAm datasets of purified cell-types.

	References 1. https://doi.org/10.1038/s41588-021-00923-x 2. https://doi.org/10.1016/j.tig.2020.08.009 3. https://doi.org/10.1038/s41467-022-33511-6 4. https://doi.org/10.1093/hmg/ddu328
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