Project Details	
Project Code	MRCNMH26Ex Mill
Title	Molecular signatures of sex differences in the human brain
Research Theme	NMH
Project Type	Dry lab
Summary	Why do males and females show different risks for brain disorders like schizophrenia, depression, autism and Alzheimer's? This project explores how sex chromosomes shape gene expression and epigenetic regulation in the human brain across development and aging. Using cutting-edge multiomic and single-cell datasets generated by our team and collaborators this bioinformatics project will investigate how the X and Y chromosomes drive molecular differences at the cellular level. You'll also examine sex-specific changes in brains affected by neuropsychiatric and neurodegenerative disease. Join our dynamic research team to uncover the biological foundations of sex differences in brain health and disease.
Description	It is well established that many brain disorders are characterised by sex differences, influencing disease prevalence, symptomatology, progression, and treatment response. For example, conditions such as autism spectrum disorder and Parkinson's disease are more prevalent in males, while Alzheimer's disease and major depressive disorder disproportionately affect females. While hormonal influences have long been recognized, emerging evidence points to sex-specific regulatory genomic mechanisms, including differences in chromatin accessibility, DNA methylation, histone modifications, and non-coding RNA expression, as being key contributors to these disparities. These regulatory differences can shape gene expression programs in a sex-dependent manner across brain development and aging, potentially conferring differential vulnerability or resilience to disease. Understanding how sex-specific epigenetic and transcriptional landscapes interact with genetic risk factors offers a powerful framework for elucidating the biological basis of sex biases in brain disorders and for informing more personalized approaches to diagnosis and therapy. This bioinformatics-focussed PhD project aims to uncover how sex-specific differences in gene regulation contribute to brain development, function, and disease. The student will leverage unique epigenomic and transcriptomic datasets generated by the supervisory teams in Exeter and Cardiff, including bulk and single-cell data from both human brain tissue and disease models. They will receive training in state-of-the-art computational approaches, including integrative multi-omic analysis and machine learning, and will work within a dynamic, collaborative environment that prioritises open and reproducible research practices. The project will be structured around three interrelated objectives, each forming the basis of a core data chapter in the PhD thesis: • Characterising sex differences across brain development and aging: The student will perform integrative analyses using existing epigenetic (DNA methylation, ATAC-seq) and transcriptomic datasets from fetal and postnatal human cortex to map sex-associated differences in gene regulation across key developmental stages and into aging. The student will be encouraged to propose novel ways of integrating datasets and source replication datasets from other groups.

	• Dissecting cell-autonomous sex effects using mosaic Klinefelter Syndrome tissue: Using a rare and uniquely powerful single-cell dataset generated from mosaic brain tissue of Klinefelter's syndrome (XXY) individuals—where both XX and XY cells are present in the same genetic and environmental background—the student will directly compare gene regulation between male and female chromosomal complements at the cellular level. This will allow unprecedented insight into sex chromosome-driven effects on gene expression and chromatin structure in the human brain. The student will take a lead role in defining analytical strategies for comparing XX and XY cells (e.g., clustering, pseudotime, or trajectory inference) and may pursue additional validation using external datasets or cell-type deconvolution methods. • Identifying sex-specific regulatory changes in brain disorders: The student will apply integrative multi-omic approaches to large-scale datasets generated in Exeter and Cardiff across a range of neurodevelopmental (e.g., autism, schizophrenia) and neurodegenerative (e.g., Alzheimer's, Parkinson's) disorders. This aim will focus on identifying regulatory elements, genes, and pathways that show sex-specific alterations in disease states, potentially highlighting mechanisms underlying sex differences in risk, progression, and therapeutic response. The student can select which disease(s) to focus on based on their interest, and explore innovative computational methods to identify novel insights. While the project is focused on testing key hypotheses and supported by available datasets, there is substantial flexibility for the student to steer the direction of the work based on their interests and findings. For example, they may choose to: focus on specific cell types (e.g., glia, neurons, immune cells) or brain regions with strong sex-bias signals; extend findings to in vitro or model systems in collaboration with experimental labs; develop or benchmark new bioinformatics tools for detecting sex effects; lead data visualisation or science communication initiatives related to the project. The student will become part of several extensive international networks via the supervisory teams role in the UK Human Functional Genomics Initiative, the APEX (autism prenatal sex differences) consortium, and the Psychiatric Genomics Consortium.
Supervisory Team	
Lead Supervisor	
Name	Professor Jonathan Mill
Affiliation	Exeter
College/Faculty	HLS
Department/School	Clinical & Biomedical Sciences
Email Address	j.mill@exeter.ac.uk
Co-Supervisor 1	
Name	Professor Nicholas Bray
Affiliation	Cardiff
College/Faculty	Division of Psychological Medicine and Clinical Neurosciences
Department/School	School of Medicine
Co-Supervisor 2	
Name	Dr Ann Babtie
Affiliation	Exeter

College/Faculty	HLS
Department/School	Clinical & Biomedical Sciences
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	