

| Project Details |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| Project Code    | NMH27Ex Mill                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Title           | From X to Y: Decoding Sex Chromosome Effects in the Human Brain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Research Theme  | Neuroscience & Mental Health                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Project Type    | Dry lab                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Summary         | <p>Why do males and females show different risks for brain disorders like schizophrenia, depression, autism and Alzheimer's disease? This project explores how sex chromosomes shape gene expression and epigenetic regulation in the human brain across development and aging. Using cutting-edge multi-omic and single-cell datasets generated by our team and international 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 differences 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.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Description     | <p>Males and females differ markedly in their risk of many brain disorders, yet the biological mechanisms underlying these differences remain poorly understood. Autism spectrum disorder and Parkinson's disease are more common in males, whereas Alzheimer's disease and major depressive disorder disproportionately affect females. While sex hormones undoubtedly contribute to these patterns, growing evidence suggests that sex chromosome complement and sex-specific gene regulatory processes may directly shape brain development, ageing and disease susceptibility. Understanding these mechanisms represents one of the major unresolved questions in neuroscience and could reveal new opportunities for precision medicine.</p> <p>This bioinformatics-focused PhD project aims to uncover how sex-specific differences in gene regulation influence brain development, function and disease. The student will analyse unique molecular datasets from the human brain, spanning fetal development through to old age and encompassing multiple genomic and epigenomic modalities. These include bulk and single-cell transcriptomic, epigenomic and multiomic datasets generated by the supervisory teams in Exeter and Cardiff, alongside data from major international collaborations. A unique feature of the project is access to rare single-cell datasets from mosaic Klinefelter syndrome (XXY) human brain tissue, enabling direct comparison of XX and XY cells within the same individual and providing an unprecedented opportunity to disentangle sex chromosome effects from environmental and hormonal influences.</p> <p>The student will receive training in state-of-the-art computational biology, including integrative multiomic analysis, statistical genetics, machine learning and reproducible research practices. They will work within a highly collaborative environment spanning neuroscience, genomics and data science, and will become part of several international research networks through the supervisory team's involvement in the UK Human Functional Genomics Initiative, the APEX (Autism Prenatal Sex Differences) consortium and the Psychiatric Genomics Consortium.</p> <p>The project will be structured around three interrelated objectives, each forming the basis of a core data chapter in the PhD thesis:</p> <ol style="list-style-type: none"> <li>1. How do molecular sex differences emerge across the human lifespan?</li> </ol> |

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|  | <p>The student will perform integrative analyses of existing transcriptomic and epigenomic datasets, including DNA methylation and chromatin accessibility data, from fetal and postnatal human brain tissue. These analyses will map sex-associated differences in gene regulation across key developmental stages and throughout ageing. The student will identify biological pathways showing sex-biased regulation, investigate how these patterns change over time, and explore their relationship to known disease risk loci. They will be encouraged to develop novel analytical approaches for integrating multiple data types and to identify external datasets for replication and validation.</p> <p>2. What are the direct effects of sex chromosome complement on human brain cells?</p> <p>Using a rare single-cell dataset generated from mosaic Klinefelter syndrome (XXY) brains, where genetically distinct XX and XY cells coexist within the same tissue environment, the student will directly quantify the impact of sex chromosome complement on gene expression, chromatin accessibility and cellular state. This unique natural experiment largely controls for environmental and hormonal variation and provides an unparalleled opportunity to identify cell-autonomous sex effects in the human brain. The student will play a leading role in developing analytical strategies for comparing XX and XY cells, including clustering, trajectory inference and network-based approaches. There will also be opportunities to validate findings using external datasets and emerging computational methods.</p> <p>3. Do sex-specific molecular pathways contribute to differences in disease risk and progression?</p> <p>The student will apply integrative multiomic approaches to large-scale datasets from neurodevelopmental and neurodegenerative disorders, including autism, schizophrenia, Alzheimer's disease and Parkinson's disease. This objective will test whether sex-specific regulatory pathways identified in healthy brain development are preferentially disrupted in disease, helping explain why these conditions show marked sex biases in prevalence, presentation and outcome. Analyses will focus on identifying genes, regulatory elements and biological pathways that show sex-dependent disease-associated alterations. The student will have flexibility to prioritise specific disorders or disease mechanisms according to their interests and emerging findings.</p> <p>Although the project is built around clearly defined scientific objectives and unique datasets, there will be substantial scope for the student to shape its direction. Depending on their interests, they may choose to focus on particular cell types, brain regions or developmental stages; develop new computational methods for studying sex effects in genomic data; explore functional validation opportunities with experimental collaborators; or extend analyses into additional disease cohorts and model systems. The student will be encouraged to take intellectual ownership of the project from an early stage and to develop independent research questions arising from their findings.</p> <p>By combining unique datasets, cutting-edge computational approaches and a high degree of intellectual freedom, this project offers an exceptional opportunity to make fundamental discoveries about one of</p> |
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|                             | the most intriguing and clinically important questions in neuroscience: why male and female brains differ in their susceptibility to disease. |
| Can be completed part time? | Yes                                                                                                                                           |
| 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 Babbie                                                                                                                                 |
| Affiliation                 | Exeter                                                                                                                                        |
| College/Faculty             | HLS                                                                                                                                           |
| Department/School           | Clinical & Biomedical Sciences                                                                                                                |
| Co-Supervisor 3             |                                                                                                                                               |
| Name                        |                                                                                                                                               |
| Affiliation                 |                                                                                                                                               |
| College/Faculty             |                                                                                                                                               |
| Department/School           |                                                                                                                                               |