| Project Details | |
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| Project Code | MRC22NMHCa John |
| Title | Interrogating the epigenetic links between prenatal adversity and increased risk of autism, schizophrenia and depression |
| Research Theme | Neuroscience & Mental Health |
| Summary | Adversity-driven epigenetic changes early in life may increase the risk of mental illness in a sex-specific manner. This study will apply state-of-the art 'omic approaches to define transcriptional and epigenetic signatures resulting from exposure prenatal depression, and compare to signatures present in samples from autism, schizophrenia and depression patients to provide novel insights into pathophysiology, and provide targets for manipulation. |
| Description | Maternal depression in pregnancy is associated with the increased risk of adverse outcomes later in life including mental illness, and with sex-specific incidence. One highly promising mechanism explaining this relationship involves adversity-driven changes to the epigenome. Epigenetic marks such as DNA methylation, unlike DNA sequences, are potentially dynamic and can be both added and removed from the genome. Critically, epigenetic marks can be “remembered” for the full lifetime of the individual and even across generations. Aberrant programming of epigenetic marks associated with genes important for fetal growth, metabolism and brain development could explain the well establish association between prenatal adversity and ill health later in life. This project will apply state-of-the art genomics approaches to define the transcriptional and epigenetic signatures of exposure to the adversity of prenatal depression and then ask whether these signatures provide insights into the pathophysiology of conditions including autism, schizophrenia and depression, and why there may be differences in the risk to males and females. Briefly, using existing data from the MRC funded Grown in Wales Study, the student will bioinformatically interrogate placental transcriptomic and genome-wide DNA methylation data to identify the molecular signature of exposure to prenatal depression. They will then generate and analyse data generated on matched cord blood DNA samples to identify epigenetic changes in newborns exposed to maternal depression, validating changes molecularly. The next step will be to integrate the Grown in Wales data with (epi)genomic studies of autism, schizophrenia and other neuropsychiatric conditions taking place at the University of Exeter. The student may then choose to continue with the same bioinformatic approaches extending their search to the ALSPAC cohort with methylation array data for children at birth from cord blood, and up to age 24 from peripheral blood. There is data on mother’s depression similar to Grown in Wales, and on children’s autism diagnoses and on depressive symptoms. The student may undertake causal inference analyses methods, such as 2-sample Mendelian randomization, where variants are used as proxies for placental DNA methylation or expression and look at its effects on the outcomes. Alternatively, the student may choose to switch to an in vivo study employing an etiological relevant and validated murine model of prenatal depression. These different options are possible because the main supervisor is principle investigator for the Grown in Wales Study, a human pregnancy cohort focused on |

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| | prenatal depression, and also undertakes work with genetically and environmentally manipulated animal models with a focus on maternal/offspring behaviour, work that is exceptionally well funded by two active BBSRC grants. Consequently there is considerable expertise to support flexibility in the project. Training across a broad range of interdisciplinary skills (developmental biology, epigenomics, bioinformatics, population-based statistics) is a particular strength of this study. The work will take place across three GW4 institutions for a direct exchange of knowledge and techniques providing a wide range of training and opportunities including use of human cohort samples (translation potential) and potential for experimental models (in vivo training). The student will gain wet lab and dry labs skills which can be reorganised to take into account events such as the recent Covid-19 outbreak. The impact of this work for human health is very clear since, in addition to addressing fundamental questions concerning the response of the epigenome to adversity in pregnancy, there is genuine potential to develop evidenced-based societal and therapeutic interventions in collaboration with clinicians, psychologists and social scientists. |
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