Project Details	
Project Code	MRCNMH24Ca John
Title	Maternal anxiety and language delays in children – both outcomes of the same epigenetic alteration?
Research Theme	Neuroscience & Mental Health
Summary	Maternal depression and anxiety are highly common in pregnancy and associated with a negative effect on the child's social and language skills. This PhD will test the novel hypothesis that both the mother's mood symptoms and her child's difficulties can stem from that same underlying molecular alteration in an epigenetically-regulated gene. Training will include population level statistics, wet lab molecular work with human tissue and in vivo experimental work.
Description	Maternal mood disorders are estimated to be present in 1 in 5 pregnancies in the UK equivalent to >150,000 births per annum with higher prevalence in socioeconomically deprived areas and some ethnic minority groups. In addition to the direct cost to the mother, maternal depression and anxiety are associated with an increased risk of adverse outcomes for children. These include low birth weight, language delays and behavioural problems more often reported for boys. Using data from the Grown in Wales study, we have discovered that male infants of anxious mothers exhibit language delays detectable as early as 12 months of age. Understanding the mechanism(s) linking the mother's mood symptoms to these distressing outcomes for her children could help the design of therapeutic interventions. It has been proposed that the mothers' mood symptoms affect the quality of her infants' early linguistic environment. However, we have developed an alternative hypothesis which is based on our observations on an in vivo model of maternal anxiety in which both maternal anxiety and deficits in pup communication originate from a single gene alteration present in the offspring. As observed in humans, the communication deficits are specific to males alongside male-specific alterations in social behaviour. This suggests that maternal mood symptoms and language delays observed in humans populations could co-occur as a result of this same gene change. The gene in question is imprinted suggesting an underlying epigenetic mechanism. This project has three related but independent elements: 1) To ask whether maternal anxiety is associated with male-specific language delays and behavioural problems in a second human cohort. The student will use data collected from >7,000 participants participating in the world-renowned longitudinal study "Children of the 90s" (also known as the Avon Longitudinal Study of Parents and Children, ALSPAC). This work can be extended to examine the role of environmental and psychosocial factors increasing risk of these conditions. 2) To determine whether expression of the imprinted PEG3 gene is associated with language development and behaviour of infants aged 12 months and 4 years. This will be achieved using biological samples from the MRC funded Grown in Wales Study, a pregnancy cohort focused on prenatal depression and infant outcomes. The student will apply a targeted approach to quantify expression of PEG3. The student may then examine DNA methylation by pyrosequencing to interogate an epigenetic mechanism. 3) To establish cause-and-effect relationships between maternal anxiety, and

	the offspring's communication and behavioural deficits. This component will utilise our mouse model of maternal anxiety. If desired by the student, there is the possibility of testing environmental and psychosocial factors identified in the human studies. A particular strength of this study is training across a broad range of interdisciplinary skills including population-based statistics, molecular and developmental biology and behavioural neuroscience. The work will take place across two GW4 institution (Cardiff and Bristol) for direct exchange of knowledge and techniques, and a wide range of training and opportunities. There is potential for advanced statistical and data analysis training and training in in vivo skills at the MRC Mary Lyon Centre. The student will gain wet and dry labs skills, and the order of work can be reorganised to take into account the student's interests and events such as Covid-19.
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