Project Details	
Project Code	MRCNMH25Ba Ward
Title	Brain growth mechanisms involving axon volume and myelination linked with autism spectrum disorder.
Research Theme	Neuroscience & Mental Health
Summary	Correct axonal volume and myelination are essential for neuronal function. Little is currently known about mechanisms controlling axon volume and loss of brain myelin occurs in ageing and common age-related neurodegenerative conditions such as Alzheimer's disease. Growing evidence also links altered myelin levels with autism spectrum disorder (ASD; affecting some 1 in 160 people worldwide). The project aims to establish the mechanisms of action for a novel regulator of axon volume and myelination that is proposed to form a link with ASD.
Description	**Significance:** Approximately 1 in 160 people are diagnosed with autism spectrum disorder (ASD), often linked with debilitating mental health conditions such as ADHD, anxiety, depression and epilepsy. Several genetic disorders and their animal models link ASD with changes in brain myelination. In the growth disorder, Silver-Russell syndrome (SRS), a sub-set of cases are associated with the imprinted GRB10 gene. Some 60% of these patients are diagnosed with ASD and associated persistent developmental delays. Consequently, though rare, SRS offers a unique opportunity to gain insights into the mechanisms underlying ASD and other common mental health disorders. **Challenge:** ASD and its comorbidities have complex genetic origins. The underlying cellular and molecular mechanisms are poorly understood. Originality: The student will use unique GRB10 mouse models of SRS that exhibit altered social behaviours that are consistent with ASD hallmarks. Preliminary data points to involvement of altered brain growth, caused by enlargement of axonal volume development and changes in myelination as a cause of these behavioural changes. Importantly, our knowledge of GRB10 suggests a testable mechanism for these cellular changes, involving regulation of insulin and mTOR signalling, potentially beginning in early embryo development. **Project Objectives:** a) Establish changes in axon volume and myelin deposition in GRB10 mutant and wild type littermate animals at different stages of brain development. b) Determine whether the cellular mechanism involves altered insulin receptor and mTOR signalling. c) Evaluate social behaviour changes in GRB10 mutant mice using new home cage video analysis techniques. d) Test for links between GRB10 and ASD or brain structural features using large-scale, genome-wide human population data. Student Ownership: There is scope for the student to explore their own ideas in pursuing each of the objectives. They will: a) Choose between various methods to examine axons, from basic histology to electron scanning microscopy and sophisticated MRI imaging. b) Decide how best to combine mouse genetics with cell biology and imaging,

	c) Select which behavioural traits to examine, along with appropriate scoring and analysis methods. d) Identify appropriate datasets and statistical approaches. **Feasibility:** The project relies on unique genetically altered mouse strains that we have developed, including 3 different strains with loss of GRB10 brain expression. Additionally, it will use large-scale human genetic datasets that have already been collected. Underpinning preliminary data includes behavioural testing, showing GRB10 mutants exhibit altered behaviours, specifically in impulsivity, risk-taking and social stability. In addition, the post-natal mutant brains accrue greater mass than wild type animals, following a time-course consistent with that of myelin deposition in the mouse brain. **Added-value features:** This project is highly inter-disciplinary, offering a rare opportunity to switch between mouse and human genetic studies and also spanning the range of biological scale, from cell and molecular to whole animal behavioural. The human genetic studies will involve the student in 'big data' analysis and the mouse genetics and behaviour will introduce in vivo skills, two of the DTP training priorities. The project spans the Neuroscience & Mental health' and 'Population Health' themes and will benefit from in-kind contributions of data, samples and reagents from the UKRI 'BrainHealth' grant held by Walton and Ward (£1.26M, 2023-2028). **Knowledge transfer:** The project aims to provide important insights into the causal mechanisms underlying ASD and other mental health conditions. The student will work with the Research and Innovation Services at the University of Bath to evidence any impact arising from the project.
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