Project Details	
Project Code	MRCNMH24Ca Isles
Title	How does the schizophrenia candidate gene Sp4 influences transcription during neurodevelopment?
Research Theme	Neuroscience & Mental Health
Summary	Both common and rare variants in the gene encoding the neuronal transcription factor Sp4 have been linked to schizophrenia. This project explores how those variants alter the ability of Sp4 to regulate the activity of the genome. The student will gain a range of sophisticated in vivo, molecular biology, and bioinformatic techniques and apply these in order unravel the biology that links Sp4 to brain function, and identify what goes wrong in schizophrenia.
Description	This project centres on understanding the molecular function of the gene Sp4, both common and rare variants in which have been linked to schizophrenia. Sp4 encodes a neuronal transcription factor and the student will investigate which genes in the genome Sp4 regulates during brain development, and how the schizophrenia associated nonsense variant affects the ability of Sp4 to control gene expression. Specifically, the primary objective are: To define the genomic targets regulated by Sp4 in the developing brain Identify how a mutation in Sp4 (Y163*), that is associated with schizophrenia, affects its ability to regulate gene expression in the developing brain Using bioinformatic techniques, explore the biology that links Sp4:Y163* to schizophrenia The initial experiments (~2.5 years) will directly address these objectives Firstly, the project will take advantage of a close partnership with MRC National Mouse Genetic Network (NMGN) cluster “MURIDAE” (led by ARI) and the MRC Mary Lyon Centre (MLC) that will provide a novel mouse model heterozygous for the Y163* nonsense variant. Under the supervision of ARI and DJB the student will perform ChIP-seq and RNA-seq studies using this model to examine differences in Sp4 binding and transcriptomics in the developing brain of wild-type and mutant mice. These experiments will be complemented by a Targeted DamID (TaDa) approach, which allows to obtain cell type-specific binding in the brain. In TaDa, Sp4 is fused to an E. coli DNA adenine methyltransferase domain (Dam). Wherever the Dam fusion protein interacts with the genome it catalyzes methylation of adenine within the sequence GATC. As endogenous adenine methylation is extremely rare in eukaryotes the genomic interaction targets can be identified by mapping adenine methylation in the genome. Under the supervision of JvdA during a placement in Cambridge, the student will learn in utero electroporation techniques, and use these to deliver wild-type and (separately) Y163* nonsense TaDa constructs to perform Sp4 TaDa-seq in the developing mouse brain in vivo. The data from these two experiments will be explored in great detail under the guidance of EH (Ex). The bioinformatic analyses will include refinement of Sp4 target genes by examining the overlap between the ChIP- and RNA-seq hits; comparison of the signal identified by ChIP- / RNA-seq in the Y163* mutant mouse model with those identified by TaDa-seq, possibly illustrating a distinction between developmental and acute effects respectively; investigation of these gene lists for enrichment of biological pathways and genes associated with schizophrenia. These experiments will give the student a range of

	cutting-edge in vivo skills, and a proficiency in data handling that is highly desirable and transferable to many careers. The student will then shape the remaining time of their PhD, having the opportunity to design experiments and pursue areas of research, within the confines of this overall project, that suit their interests. For instance, options could include additional whole animal in vivo research including neurodevelopmental, neurophysiology, or behavioural studies (allied to the NMGN MURIDAE cluster and conducted within the MLC), or further molecular work using human iPSCs to provide converging evidence from other model systems. The student will have opportunities to present their work outside of the GW4. For instance, the student will be encouraged to attend and present at the MRC NMGN research events that will be held at the MLC and present their findings at student seminars within the Department of Clinical Neurosciences at the University of Cambridge. Additionally, as part of our programme of work, we will have a symposium highlighting the work of the MURIDAE cluster at the BNA Festival of Neuroscience in 2025; this will be an opportunity for the student to give a talk at an international conference.
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