Our lab is investigating a model in which, FMRP hinders ribosome movement on mRNAs regulating protein expression. Removal of FMRP results in faster ribosome movement and more protein production. In this study we identified a number of neuronal mRNAs on which FMRP blocks ribosome movement, for example, SETD2. Indeed, an increase in SETD2 protein levels is found upon loss of FMRP. We further studied the downstream consequence of increasing SETD2 levels and found genome wide alteration of epigenetic marks that are deposited by SETD2. Furthermore, this change in epigenetic marks also affects the mRNAs produced from these genomic loci by leading to differential alternative splicing changes.

In a nutshell, upon deletion of the FXS causative gene, Fmr1, we find widespread defects in epigenetic marks and alternative splicing of mRNAs required for proper brain function. These findings align with those previously made in Autism patients. Understanding similarities and differences between FXS autism might aid in better detection and designing of therapeutics for intellectual disabilities.

Autism Spectrum Disorder (ASD) is an intellectual disability that results in mild to severe cognitive impairments and is found to occur in 1 in 54 children. About 15% of autism cases can be attributed to genetic causes and the most prevalent amongst these is the Fragile X syndrome (FXS). In FXS, a single gene on the X chromosome called the FMR1 gene is ‘switched off’ which results in loss of the protein, FMRP. FMRP binds mRNAs and ribosomes that translate the mRNAs into protein products.