Understanding the Molecular Etiology of Rett Syndrome

Zhaolan (Joe) Zhou, PhD
University of Pennsylvania
Basic Research Grant
$75,000

Scientific Abstract:

Rett Syndrome (RTT) is a neurodevelopmental disorder that occurs almost exclusively in girls and represents one of the leading causes of intellectual disabilities. RTT is caused by heterozygous mutations in the X-linked gene encoding MeCP2, a methyl-CpG binding protein thought to modulate gene transcription. Previous studies reported that MeCP2 binds to chromatin broadly throughout the genome and regulates hundreds of genes in the brain. We found that the effect of MeCP2 on gene transcription is both cell type-specific and mutation type-dependent. However, most of these studies are conducted in male mouse models of RTT, partially because random X-chromosome inactivation (XCI) leads to mosaic expression wild- type (WT) and mutant MeCP2, leaving identification of MeCP2 bona fide molecular targets in heterozygous females difficult. Given that RTT is a female disorder with mosaic MeCP2 expression, we recently developed a Cre-dependent biotinylation strategy to tag MeCP2, either in WT or mutant form, with biotin, thus allowing us to distinguish and isolate MeCP2 mutant- expressing cells from WT-expressing cells in heterozygous female brains. We propose to take advantage of this strategy to investigate the cell and non-cell autonomous effect of MeCP2 on gene expression in female mouse models of RTT. We hope to ultimately gain insight into the molecular etiology of RTT and uncover new therapeutic strategies specific to RTT.