Embryonic ablation of *Atrx* in excitatory neurons results in memory deficits and autistic-like behaviours in adult mice

Katherine Quesnel[1,2,4], Nicole Martin-Kenny[1,2,4], Jacob Ellegood[5,6], Jason P. Lerch[5,6] and Nathalie G. Bérubé[1,2,3,4]

Affiliations: [1]Department of Anatomy & Cell Biology, [2]Department of Paediatrics, and [3]Department of Oncology, Western University, London, Canada. [4]Division of Genetics & Development, Children's Health Research Institute, London ON, Canada. [5]Mouse Imaging Centre, The Hospital for Sick Children, Toronto, Canada. [6]Department of Medical Biophysics, The University of Toronto, Toronto, Canada.

Previous reports show mutations in chromatin remodeling proteins are prevalent in patients of intellectual disability and autism. Furthermore, 70% of patients with autism also have intellectual disability. Overlapping features and often comorbidities in diagnosis in patients suggests an overlap in regions of the brain that have developed atypically. In this study, we examine the function of the gene alpha thalassemia mental retardation, X-linked (ATRX), a chromatin remodeling protein. Hypomorphic mutations in ATRX result in ATR-X-syndrome, a disorder characterized by severe intellectual disability with presenting autistic features. Mice lacking ATRX specifically in excitatory neurons starting from embryonic day 11.5 were generated to study effects of loss of ATRX in differentiated excitatory neurons early during brain development. Loss of ATRX in excitatory neurons embryonically resulted in a decrease in contextual fear memory, along with hyperactive and repetitive behaviours (over-grooming). Male mice displayed a prominent aggressive phenotype, whereas female mice displayed social avoidant behaviours. Male adult mice also displayed a significant acoustic startle response that was absent in adult female mice. Magnetic resonance imaging (MRI) analysis revealed decreased relative brain volumes in the hippocampus, cerebellum and white matter regions, whereas regions of the cortex and thalamus had significant increased relative brain volumes. We conclude that neuronal ATRX plays a critical role during early brain development in excitatory neurons to prevent memory deficits and autistic features. MRI data suggests that loss of ATRX early in brain development results in atypical brain structure and possible disruption of the neuronal circuitry.