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Title: ALR-1/ARX REGULATES SYNAPTOGENESIS AND GABAERGIC NEURONAL DIFFERENTIATION BY DISTINCT TRANSCRIPTIONAL REGULATORY PATHWAYS

Abstract:
Intellectual disabilities arise from disruption of normal brain function. ARX is a transcription factor known to regulate brain development and patterning, which has been shown to cause an X-linked form of intellectual disability and other syndromes associated with neurological deficits. Moreover, several mutations have been identified in this gene, and there is a correlation between the class of mutation and the resulting neurological syndrome. This gene is conserved throughout evolution, and mutations in the Caenorhabditis elegans ortholog, alr-1, result in defects in neuronal development. We discovered that these defects can be rescued by human ARX, creating an ideal model system to test the biological underpinnings of ARX disease-causing mutations. Furthermore, alr-1 is differentially regulated in subgroups of neurons, suggesting a complex regulatory mechanism behind alr-1 neuron-specific function and possibly explaining the genotype/phenotype correlation observed in ARX mutations. Additionally, genetic analyses of candidate alr-1/ARX targets support its role in regulating synaptogenesis and GABAergic neuronal differentiation. Current work aims at (1) identifying the regulatory sequences responsible for neuron group-specific expression of alr-1 and (2) identifying its target genes.