Studies on the chromatin regulatory factor ASH1L in human neuronal development

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Autism spectrum disorders (ASD) are associated with defects in neuronal connectivity and are highly heritable. A significant proportion of ASD cases are of complex genetic etiology, this complexity might reflect the impact of gene-environment interactions. However, there is a gap in our understanding on the mechanisms that underlie the gene-environment interaction in autism complex etiology. Genetic findings suggest that there is an overrepresentation of chromatin regulatory genes associated with autism. This suggests that ASD environmental risk factors might exert their effect by modulating epigenetic mechanisms that alter neuronal circuitry development. Genetic studies have identified ASH1L a histone methyltransferase as a high-ranking candidate gene for autism risk. We find that ASH1L is strongly downregulated in human neurons by Valproate (VPA) treatment. VPA is one of the most robust environmental autism risk factors. ASH1L dimethylates Histone H3 on Lysine 36 (H3K36me2), this histone mark has been implicated in both transcriptional activation and repression. Therefore, ASH1L could differentially modulate expression of genes relevant to ASD in response to the environment. However, how mutations in ASH1L lead to deficits in neuronal connectivity associated with autism pathogenesis is not known. We are using genome editing and shRNA knockdown approaches to interrogate the function of ASH1L in stem cell derived human neurons. Our preliminary data suggests that knockdown of ASH1L in human neurons might alter the expression of various chromatin regulatory and transcription factors that are relevant for neuronal function in stem cell derived human neurons.