

Regulation of chromatin accessibility and Pet1/FEV binding during serotonergic (5-HT) neuron development

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Serotonin (5-HT) is implicated in the pathophysiology of many neuropsychiatric disorders, including depression, anxiety, and autism. During development, transcription factors such as the ETS domain TF Pet1 (human ortholog FEV) activate 5-HT specific gene expression programs that, in turn, enable 5-HT neurons to acquire their neurotransmitter identity and adult characteristics. In addition to sequence specific transcription factor binding, proper gene expression also depends on the opening and closing of chromatin. The open chromatin landscape can act as a cell type specific filter to define the accessibility of the genetic blueprint to the transcriptional machinery. Currently, little is known about the 5-HT neuron epigenetic landscape. Here, we hypothesize that the chromatin architecture of 5-HT neurons dynamically changes, which impacts TF-DNA interactions and the expression of genes essential for 5-HT neuron identity. To investigate this hypothesis, we adapted Assay for Transposase-Accessible Chromatin coupled to high throughput sequencing (ATAC-seq) to 5-HT neurons and other hindbrain cells, and generated highly reproducible maps of the open chromatin landscape during stages of mouse embryonic development. We found that 5-HT neurons have distinct open chromatin patterns that distinguish them from other hindbrain cells, and that 5-HT neurons of different developmental stages are distinguishable by their unique chromatin signatures. We also find that dynamically remodeled 5-HT chromatin regions are enriched for the GGAA/T binding motif of ETS domain transcription factor Pet1 that is important for 5-HT specific gene expression. Investigating how 5-HT chromatin remodeling impacts TF-DNA interactions will elucidate the molecular programs shaping 5-HT neuron development, which is important for our understanding of many neuropsychiatric disorders.