Background and Introduction

To investigate the roles of the two genes in the D1-SPNs, we deleted Foxp1 and/or Foxp2 from the D1-SPNs and then performed: a battery of behavioral tests, single-nucleus RNA-Seq experiments (snRNA-Seq) of striatal tissue, or electrophysiological experiments. An AAV-mediated injection of Foxp1/2 into D1-SPNs was performed in a subset of mice.

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References


Robustness between FOXP transcription factors maintains striatal function

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Abstract

Variants in the transcription factors FOXP1 and FOXP2 are significantly associated with autism spectrum disorder (ASD) and expressive language impairments. Both genes are expressed in spiny projection neurons (SPNs) in the striatum, where they may work together to regulate gene expression. Knockout of Foxp1 from the dopamine 2 receptor (D2) SNPs in mice results in significant behavioral, morphological, and physiological impairments, while there are fewer changes in all of these domains upon deletion of Foxp2 from D1 dopamine receptor (D1) SNPs. This difference may be due to the differential expression of Foxp1 and Foxp2 in the SNPs; Foxp1 is highly expressed in both D1 and D2 SNPs whereas Foxp2 is more highly expressed in the D1 SNPs relative to D2 SNPs. Therefore, we hypothesize that Foxp1 and Foxp2 have compensatory functions in the D1 SNPs. Utilizing mice that have a Drd1 specific knockout of Foxp1, Foxp2, or both genes, we find that loss of both genes results in impaired motor learning, hypoxic activity, and social behavior as well as increased firing of the D1 SNPs. Differential gene expression analysis from single nucleus RNA-sequencing implicate genes involved in ASD risk, maintenance of electrophysiological properties, and neuronal development and function. These data support the hypothesis that Foxp1 and Foxp2 functionally compensate for each other in D1 striatal neurons.

Experimental Design

SnRNA-Seq of Juvenile Striatum

Loss of both Foxp1 and Foxp2 results in KLeak mediated hyperexcitability

Conclusions

- Differentially expressed genes (DEGs) from D1-SPNs of both juvenile and adult knockout are involved in mediating electrophysiological properties and cell soma
- The γKash channel, K0.2 is downregulated in Foxp1KO and Foxp2KO D1-SPNs.
- Loss of Foxp1 results in hyperexcitability of the D1-SPNs, efficiently compensated with further loss of Foxp2. Loss of only Foxp2 results in hyperexcitability.
- Neuronal hyperexcitability driven by impairments in γKash channels.
- Re-expression of Foxp1 into Foxp2 KO D1-SPNs rescues excitability phenotype.
- Motor impairments in adult mice only seen upon the loss of both Foxp1 and Foxp2 from the D1-SPNs. Knockout of Foxp1 results in a social behavior deficit. This impairment is amplified upon the further loss of Foxp2.
- Exogenous expression of Foxp1 rescues behavioral impairments.