Characterization of Cortical Development in Mouse Models of Neurofibromatosis Type-1 and Elevated ERK/MAPK Activity

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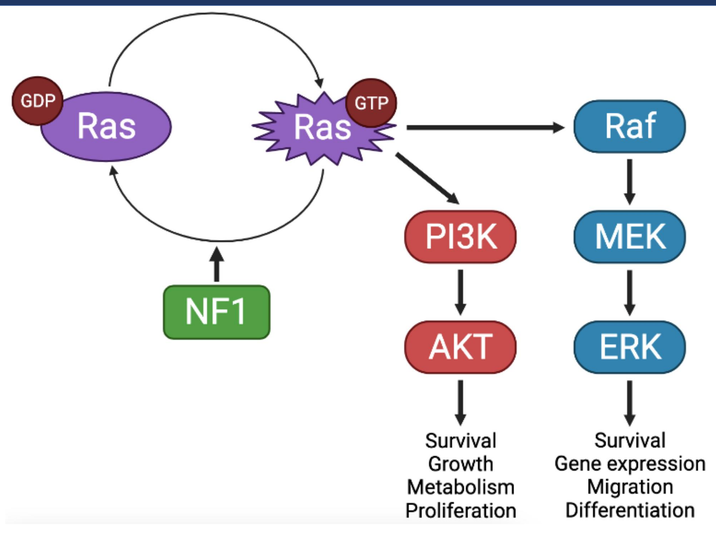
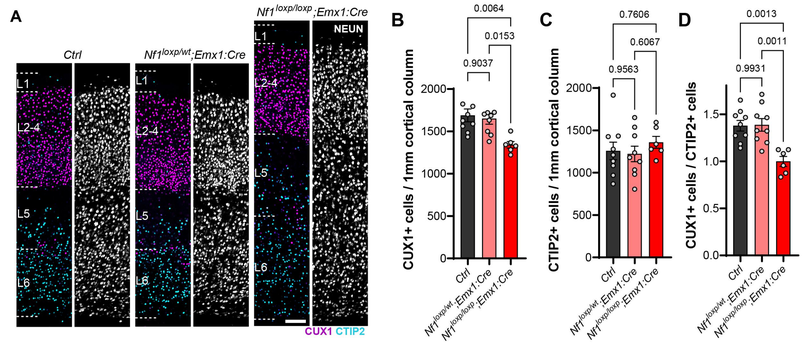
Abstract

Neurofibromatosis type-1 (NF-1) is a common neurodevelopmental disorder characterized by a range of symptoms including neurofibromas and cognitive deficits. Neurofibromin (NF1), the protein expressed by the *NF1* gene, is an important regulator in the Ras signaling pathway, and the precise mechanisms by which NF1 deficiency leads to the pathogenesis of the NF-1 cognitive phenotype is not well understood. The present study aimed to address this knowledge gap by investigating the effects of NF1 deficiency on cortical neuron and oligodendrocyte development, exploring both the impact of decreased *NF1* expression and isolated upregulation of downstream signaling pathways on cortical development. We used a combination of *Nf1* conditional knockout (cKO) mouse models and mouse models exhibiting ERK/MAPK hyperactivity–a critical signaling pathway downstream of Ras–to model the biochemical expression of NF-1, and immunolabeling for layer-specific neurons and oligodendrocytes at different developmental stages were used to quantify changes in cortical development. In our NF1 deficient model, we identified both a reduction of upper layer excitatory neuron density and an overproduction of oligodendrocyte progenitor cells (OPCs) within the cortex. However, despite identifying a similar reduction of upper layer excitatory neuron density in our hyperactive ERK/MAPK model, we observed only a slight increase in OPC density as compared to the *Nf1* cKO models. To explore how the developmental trajectory of neurons and oligodendrocytes are affected by decreased NF1 production and the resulting upregulation of the ERK/MAPK signaling pathway, we performed EdU pulse labeling, ultimately identifying signs of precocious neurogenesis and gliogenesis in both models. Collectively, these results further characterize the effects and mechanisms by which decreased NF1 production affects cortical development.

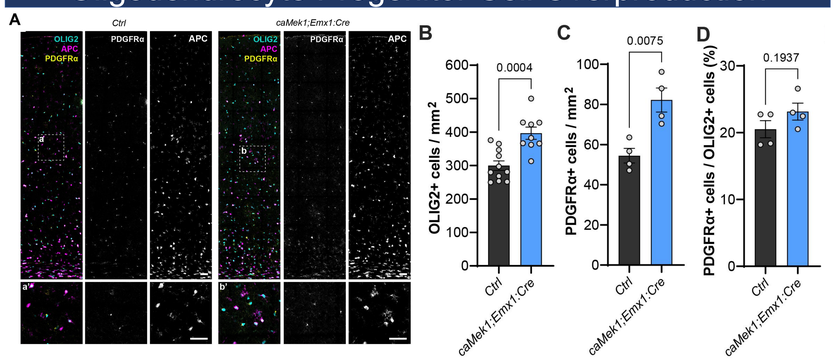
NF1 Downregulates Ras Signaling Activity



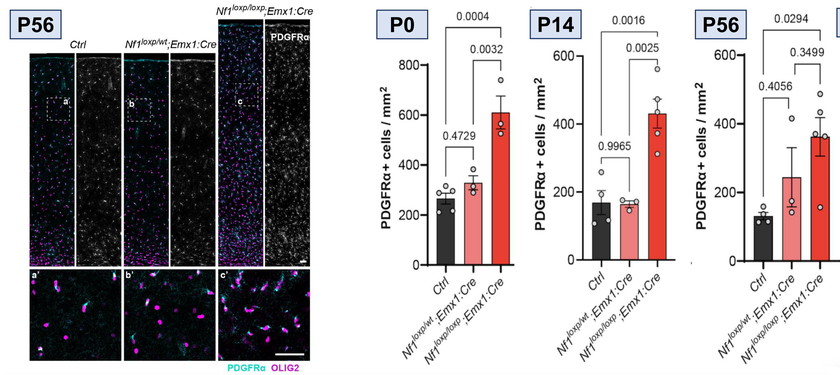
Nf1 Inactivation Reduces Number of Upper Layer Neurons



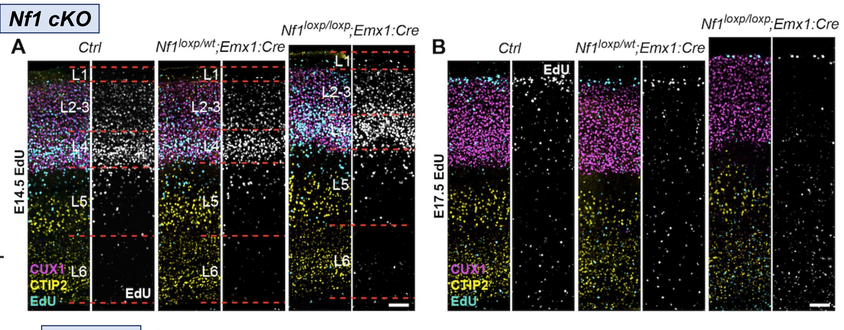
ERK/MAPK Hyperactivity Yields Reduced Oligodendrocyte Progenitor Cell Overproduction



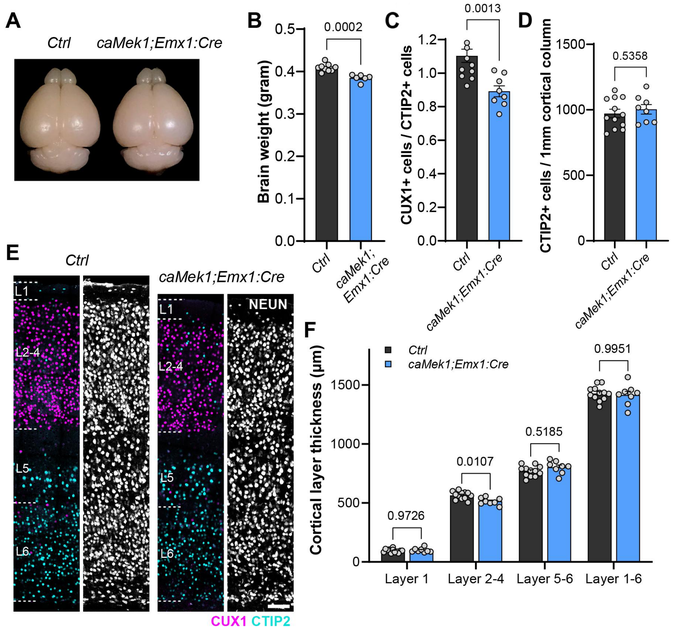
Nf1 Inactivation Results in Oligodendrocyte Progenitor Cell Overproduction



Nf1 Inactivation and ERK/MAPK Hyperactivity Result in Precocious Neurogenesis and Gliogenesis



ERK/MAPK Hyperactivity Recapitulates the NF-1 Neuronal Phenotype



Discussion

- Verifies past findings & offers novel insight into neuronal & oligodendrocyte development in NF-1
- Precocious neurogenesis results in precocious gliogenesis, potentially offering insight into observed cortical neuronal and oligodendrocyte phenotype
  - Early transition may result in decreased consumption of neural stem cells in neurogeneisis, providing increased amounts for gliogenesis
  - More time for gliogenesis could result in increased oligodendrocyte production
- ERK/MAPK pathway sufficient to result in neuronal phenotypes, not sufficient to fully recapitulate oligodendrocyte overproduction
  - Sufficient to drive precocious neurogenesis
  - Supports previous findings that ERK/MAPK drives cellular differentiation, but it's likely that PI3K/AKT hyperactivity is needed to drive overproduction