INVESTIGATING THE ROLE OF EBF3 HAPLOINSUFFICIENCY WITHIN THE DEVELOPING MURINE CEREBELLUM

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Background: Neurodevelopmental disorders (NDD) affect 53 million children globally. Although diverse types of NDD exist, there may be common underlying disease mechanisms. These mechanisms include dendritic spine abnormalities, excitation-inhibition imbalance, aberration of epigenetic regulators, and perturbation of brain structures. Cerebellar abnormalities such as cerebellar vermian hypoplasia, cortical volume loss, and foliation defects are frequently associated with NDD. Therefore, monogenic causes of NDD with co-morbid cerebellar dysfunction may serve as useful models to delineate the critical regulatory networks and developmental timeframes that underlie NDD pathogenesis. Early B-Cell Factor 3 (EBF3), a member of the Collier/Olf/Early B-Cell Factor (COE) transcription factor family, was identified as a monogenic cause of NDD. EBF3 haploinsufficiency is associated with 10q26-deletion syndrome (MIM#609625), which is characterized by facial dysmorphisms, short stature, urogenital anomalies, motor impairments, intellectual disability, cerebellar hypoplasia, and comorbid autism spectrum disorder. Single gene deletion and heterozygous EBF3 loss-of-function variants cause the Hypotonia, Ataxia, and Delayed Development Syndrome (HADDS, MIM#617330), which shares many features with 10q26-deletion syndrome. Cerebellar abnormalities are the most common structural brain finding in both conditions, making EBF3 a prime target for dissecting cerebellar development and its relation to NDD.

Materials/Methods: Constitutive heterozygous Ebf3 null mice exhibit disrupted cerebellar development and behavioral perturbations analogous to findings in the human conditions. To further study the region and cell-type specific role of Ebf3, we generated a novel conditional Ebf3 flox mouse model (Ebf3flox). We used either Nestin-Cre (CNS) or Engrailed 1-(EN1)-Cre (midbrain, rostral hindbrain, cerebellum, V1 spinal interneurons) mice in combination with Ebf3flox/+ to delete one Ebf3 allele from either the entire CNS or primarily from the cerebellum. To identify the spatiotemporal expression of Ebf3 within the developing cerebellum and trace the lineage of Ebf3 expressing neurons, we have developed a novel CRISPR Ebf3-P2A-eGFP::iCre knock-in mouse model.

Results: Sanger sequencing will be used to confirm genomic insertion.

Conclusions: Neuroanatomical, molecular, electrophysiological, behavioral, and transcriptomic studies using these tools will provide further insight regarding how Ebf3 regulates cerebellar development and function.

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