ELUCIDATING THE ROLE OF EBF3 HAPLOINSUFFICIENCY IN 10Q26 DELETION AND HADD SYNDROME PATHOGENESIS

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Background: Early B-cell factor 3 (EBF3) encodes a transcription factor belonging to the Collier/Olf/EBF (COE) family. COE factors are crucial for survival and nervous system development. Large genomic deletions containing EBF3 are associated with a neurodevelopmental disorder known as 10q26 deletion syndrome (MIM #609625) and either heterozygous single gene EBF3 deletions, intronic variants, or missense variants cause the Hypotonia, Ataxia, and Delayed Development Syndrome (HADDS) (MIM #617330). HADDS is characterized by hypotonia, ataxia, global delayed development, motor incoordination, short stature, cognition ranging from neurotypical to mild to moderate impairments, impaired expressive language, hypomimia, altered sensory processing, autistic features, and other neuropsychiatric comorbidities. Brain imaging studies in individuals with HADDS commonly reveal cerebellar vermian hypoplasia. Several phenotypic features seen in HADDS overlap with those in 10q26 deletion syndrome, indicating that EBF3 haploinsufficiency is deleterious.

Materials/Methods: We generated a constitutive mouse Ebf3 null allele by using CRISPR-Cas9 to delete exons two through four and backcrossed this allele at least four generations to the C57BL/6J strain. Brain morphology was analyzed in fixed brain tissue from postnatal day 0 to 6-weeks old mice. General health was assessed weekly for a year. Behavioral phenotyping assays testing for anxiety, motor coordination, social behavior, cognition, and sensory processing were employed. Findings were compared to age- and gender-matched wildtype littermate controls.

Results: All genotypes are born at the expected Mendelian ratio. There is a 33% reduction in perinatal viability in heterozygous mice and 100% perinatal lethality in homozygous null mice. RNA, Western blot, and immunohistochemistry analysis confirms loss of Ebf3 expression in heterozygous and homozygous null mice. Neuroanatomical studies reveal that Ebf3 haploinsufficiency causes cerebellar hypoplasia and abnormal cerebellar foliation. General health and behavioral assessments reveal reduced body size, dystonia, motor impairments, decreased anxiety-like behavior, increased sociability, and abnormal sensory processing in heterozygous mice.

Conclusions: Together, our findings show that Ebf3 haploinsufficiency perturbs neurodevelopment in mice and recapitulates cardinal features of EBF3-related disorders. Ongoing studies will identify the molecular and neurophysiologic mechanisms underlying EBF3-related neurodevelopmental disorders.