ELUCIDATING EBF3 GENETIC MODIFIERS AND HEDGEHOG SIGNALING IN EBF3-RELATED NEURODEVELOPMENTAL DISORDERS THROUGH CROSS-SPECIES APPROACHES

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Background: EBF3 (Early B Cell Factor 3) belongs to the evolutionarily conserved COE (Collier/Olf/EBF) family of transcription factors critical for differentiation of neuronal populations and essential for survival. Heterozygous loss of EBF3 function results in the Hypotonia Ataxia and Delayed Development Syndrome (HADDS) and is associated with 10q26 deletion syndrome. Recurrent EBF3 variants were identified affecting p.R163, a key residue in the zinc finger motif required to stabilize interaction with DNA. Previously, we showed that expression of human EBF3 WT rescued the lethality caused by the loss of the fruit fly homolog, knot, which indicates functional conservation. However, expression of EBF3 p.R163Q in fruit flies failed to rescue knot LOF lethality. Intriguingly, we found that EBF3 WT or EBF3 p.R163Q overexpression differentially affects the cross-vein pattern formation, suggesting disrupted hedgehog (hh) signaling. In fruit flies, knot is a known mediator of hh-signaling. The mammalian homolog Sonic hedgehog is critical for nervous system development and cell-type specification. Our hypothesis is that Hh signaling may be a key component of the EBF3-mediated gene regulatory networks.

Materials/Methods: An RNAi based modifier screen was performed in fruit flies to identify potential modifiers of the EBF3-mediated wing vein phenotype. To determine the involvement of hh-signaling, qPCR analysis of hh-signaling components and targets were performed in postnatal day 0 EBF3 +/- mice hindbrain and kn mutant fly embryos.

Results: The RNAi based modifier screen in fruit flies identified several modifiers of the EBF3-mediated wing vein phenotype. qPCR analysis showed significant reduction in hh pathway components and targets in EBF3 +/- mice hindbrain and kn mutant fly embryos.

Conclusions: Our initial findings in fruit flies and mice reveal EBF3 regulates multiple components of the hh-signaling pathway, and these findings will pave the way for unraveling the pathogenic mechanisms underlying EBF3-related neurodevelopmental disorders.