NEUROFUNCTIONAL AND NEUROANATOMICAL MARKERS OF EBF3-RELATED NEURODEVELOPMENTAL DISORDER

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Background: Early B-cell factor 3 (EBF3) is located on chromosome 10q26.3 and is a member of the Collier/Olfactory-1/EBF (COE) family of transcription factors, which play an essential role in nervous system development. Heterozygous EBF3 whole-gene deletion has been associated with 10q26-deletion syndrome and single-gene variants cause Hypotonia, Ataxia, Delayed Development Syndrome (HADDS). HADDS is an autosomal dominant neurodevelopmental disorder (NDD) with broad clinical features, including neurological abnormalities. To date, information on HADDS has been limited to clinical observations and the disease spectrum remains to be fully defined. In this study, we quantified neurocognitive performance, neurobehavioral function, and neuroanatomical findings in individuals with HADDS to investigate brain function deficits, identify vulnerable brain regions, and uncover genotype-phenotype associations.

Materials/Methods: The current sample includes 15 participants ages 5 to 14 (M = 8.73, SD = 3.24). The affected group (10 males and 2 females) includes individuals with a molecular confirmation of a pathogenic EBF3 variant or gene deletion (9 de novo and 3 inherited variants), and the control group includes neurotypical siblings (2 males, 1 female). We used neuropsychology assessments to measure neurocognitive performance in affected individuals compared to neurotypical siblings and normative population datasets. To determine neuroanatomical alterations, we conducted volumetric analyses using retrospective MRI data. Finally, we used genetic testing results to identify EBF3 variant type and determine associations between genotype, neurocognition, and volumetric quantification of affected brain regions.

Results: Affected individuals showed significant neurocognitive alterations in executive functioning, social functioning, sensory processing, and adaptive functioning domains compared to normative population datasets and neurotypical sibling controls. They also showed significantly reduced cerebellar volume relative to total brain volume. We observed a trend toward variant-specific effects of cognition and behavior. Study enrollment is ongoing.

Conclusions: These results may improve cognitive remediation strategies specific to children with EBF3-related NDD, such as HADDS, determine brain regions impacted by EBF3 dysfunction, and delineate neurogenetic substrates responsible for cognition and behavior. These findings have the potential to facilitate prognostication and personalized therapeutic strategies.

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