

EXPANDED PHENOTYPIC PROFILING ENABLES SYSTEMATIC SCREENING FOR PATHOGENIC EBF3 VARIANTS IN HADD SYNDROME

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Background: Hypotonia, Ataxia, and Delayed Development Syndrome (HADDs) is a neurodevelopmental disorder caused by heterozygous Early B-cell Factor 3 (EBF3) loss-of-function variants or gene deletions. This disease is characterized by a distinct set of clinical features, but the frequency and severity of specific features cannot be reliably determined from literature review alone due to variation in reporting and documentation. Therefore, consistent in-depth analysis of a large HADDs cohort at a single institution will reduce the time to diagnosis, elucidate the spectrum of severity, facilitate prognostication, and identify potential avenues for therapeutic interventions.

Materials/Methods: We performed a deep phenotypic analysis of 26 individuals with HADDs evaluated at Texas Children's between 2017 and 2019. There were 23 common features identified, six of which (hypomimia, pain insensitivity, weak or absent cry in neonate, hypotonia, ataxia, and developmental delay) were highly predictive of HADDs when seen concurrently. We developed a screening procedure to evaluate the likelihood of a positive HADDs diagnosis and determine whether a targeted EBF3 gene test is warranted. We ran this procedure on our study cohort, the published literature of 30 patients with HADDs, and 15 patients with CDC42-related Takenouchi-Kosaki Syndrome (TKS). We also developed a severity scale based on brain MRI findings, motor function, and language ability.

Results: Our phenotypic analysis revealed that the majority of individuals with HADDs have age-appropriate cognition based on receptive language, IQ, and performance in mainstream education, indicating that cognitive impairments are less severe than presented in the current literature. The screening system recommended a targeted EBF3 test for 92% of the HADDs patients in this study, 63% of HADDs patients in the literature, and no TKS patients. The most-severe symptoms in HADDs were associated with missense variants in the Zinc Finger (ZNF) motif, consistent with prior findings demonstrating that the ZNF is critical for stabilizing the interaction of EBF3 with DNA.

Conclusions: We developed an efficient and reproducible clinical screening procedure for a rapid and cost-effective diagnosis, identified a robust genotype-to-phenotype correlation for pathogenic EBF3 variants and disease severity, and expanded the phenotypic spectrum of EBF3-related HADDs.