
ELONGATOR FUNCTION IN THE ANTERIOR PITUITARY AND ITS RELEVANCE TO FAMILIAL DYSAUTONOMIA

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Familial Dysautonomia (FD) is a devastating neurodegenerative childhood disease characterized by a diminished number of autonomic neurons. FD children suffer from a multitude of autonomic symptoms including cardiovascular instability, gastrointestinal incoordination, and respiratory dysfunction. FD patients also exhibit an abnormal autonomic stress response, show poor growth velocity, and have difficulty gaining and maintaining weight. Treatment with growth hormone (GH) has been shown to increase growth velocity in FD patients. FD results from a mutation in the *IKBKAP* gene and diminished levels of the corresponding protein IKAP, a scaffolding protein that assembles a multi-subunit complex called Elongator. Elongator functions in the modification of tRNAs that mediate translation of AA- and AG-ending codons including lysine, glutamine, and glutamic acid. In the absence of Elongator, small AG biased genes are upregulated and large AA-biased genes are downregulated. IKAP is expressed throughout the autonomic nervous system and historically

FD has been considered a strictly neurological disease. Here we show that IKAP is robustly expressed in the pituitary gland, indicating a strong dependence on Elongator. We hypothesize that compromised growth in FD may actually result from dysfunction of somatotrophs in the anterior pituitary, a non-neuronal cell type. To test this hypothesis, we generated a conditional knockout (CKO) mouse where *Ikbkap* is selectively ablated in anterior pituitary somatotrophs. These CKO mice exhibit decreased growth compared to control littermates. Surprisingly, quantitative immunohistochemistry indicates that GH1 levels may actually be increased in the CKO pituitary. CaBP7, a calcium binding protein that negatively regulates vesicle trafficking, is also found at elevated levels in the CKO, likely because of its strong AG-bias. In combination, these results suggest that upregulation of CaBP7 may inhibit GH1 exocytosis from pituitary cells, decreasing the amount of circulating GH1 and compromising growth in FD patients.