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A new *Drosophila* model of Ubiquilin knockdown shows the effect of impaired proteostasis on locomotive and learning abilities

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Abstract

Ubiquilin (UBQLN) plays a crucial role in cellular proteostasis through its involvement in the ubiquitin proteasome system and autophagy. Mutations in the *UBQLN2* gene have been implicated in amyotrophic lateral sclerosis (ALS) and ALS with frontotemporal lobar dementia (ALS/FTLD). Previous studies reported a key role for UBQLN in Alzheimer's disease (AD); however, the mechanistic involvement of UBQLN in other neurodegenerative diseases remains unclear. The genome of *Drosophila* contains a single *UBQLN* homolog (*dUbqn*) that shows high similarity to *UBQLN1* and *UBQLN2*; therefore, the fly is a useful model for characterizing the role of UBQLN *in vivo* in neurological disorders affecting locomotion and learning abilities. We herein performed a phenotypic and molecular characterization of diverse *dUbqn* RNAi lines. We found that the depletion of *dUbqn* induced the accumulation of polyubiquitinated proteins and caused morphological defects in various tissues. Our results showed that structural defects in larval neuromuscular junctions, abdominal neuromeres, and mushroom bodies correlated with limited abilities in locomotion, learning, and memory. These results contribute to our understanding of the impact of impaired proteostasis in neurodegenerative diseases and provide a useful *Drosophila* model for the development of promising therapies for ALS and FTLD.

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