Investigating mechanisms of UBQLN2-mediated neurodegenerative disease

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Research Abstract

? DESCRIPTION (provided by applicant): Ubiquilin2 (UBQLN2) is one of a family of closely related ubiquilin proteins recently implicated in a wide range of neurodegenerative diseases including Alzheimer’s disease, Lewy Body Dementia, Frontotemporal Dementia and Huntington’s Disease. Mutations in the UBQLN2 gene also directly cause an inherited fatal neurodegenerative disorder that spans the Frontotemporal Dementia/Amyotrophic Lateral

Sclerosis (FTD/ALS) spectrum and is associated with accumulation of the RNA binding protein TDP43. The involvement of ubiquilins in numerous degenerative brain diseases reflects the fact that these proteins are believed to normally help maintain neuronal protein homeostasis, but their function in health and disease is still poorly understood. The objective of the current proposal is to leverage a valuable new research tool — transgenic mouse lines expressing wild type or pathogenic (mutant) UBQLN2 — to advance scientific understanding of the role of ubiquilins in a wide variety of neurodegenerative diseases, ranging from common synucleinopathies, amyloidopathies, and TDP43 proteinopathies to rarer diseases such as UBQLN2-mediated FTD/ALS. These new models are expected to accelerate discoveries about both the normal role of UBQLN2 in neurodegenerative proteinopathies and the mechanism by which mutations in this quality control protein cause FTD/ALS. The proposal has two aims that build on newly generated transgenic mouse lines, preliminary results showing robust aggregate pathology selectively in mutant UBQLN2-expressing mice, and a screen for interacting proteins that suggests UBQLN2 forms complexes with two closely related ubiquilins, UBQLN1 and UBQLN4. The first aim will seek to define the neuropathological features in transgenic mice expressing wild type or mutant UBQLN2. The second aim will assess motor, behavioral and electrophysiological changes in wild type and mutant UBQLN2 transgenic mice. The studies proposed here are expected to answer fundamental questions about normal and mutant UQBLN2 behavior and, more broadly, about the role of ubiquilins in brain health and disease, that could have important ramifications for therapeutic strategies.

Further information available at:

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