Cell autonomous and non-cell autonomous roles of the GWAS risk factor BIN1 in Alzheimers disease neuropathology

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Alzheimer's disease & other dementias

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Research Abstract
This proposal focuses on BIN1, one of the recently identified common risk genes within the major susceptibility loci for late-onset Alzheimer's disease (LOAD) (second only to APOE). BIN1 (Bridging INtegrator-1) is a member of a family of adaptor proteins that regulate membrane dynamics in the context of endocytosis and membrane remodeling. Alternate splicing of the 20 exons in BIN1 gene generates ubiquitous and tissue- specific isoforms, which differ in their tissue distribution, subcellular localization, and function. These functions include cell cycle progression, apoptosis, cytoskeletal organization, and DNA repair. An increase of BIN1 expression and alternate splicing of BIN1 have been reported in the brains of individuals with LOAD but how these observations translate to increased risk for AD is entirely not clear. In preliminary studies, we have characterized prominent BIN1 expression in mature oligodendrocytes in the gray and white matter in rodent and the human brain. By generating oligodendrocyte-specific Bin1 conditional knock out (cKO) mice, we confirmed that BIN1 is mainly expressed in mature oligodendrocytes. Interestingly, we observe aberrant BIN1 expression near human senile plaques and BIN1 accrual in amyloid deposits of AD transgenic mouse models. Based on these novel findings, we hypothesize that BIN1 functions in mature oligodendrocytes, and that alteration in BIN1 expression and/or function in oligodendrocytes plays a role in AD-related pathogenic processes and neurodegeneration in a non-cell autonomous manner. We propose the following specific aims to test novel hypothesis related to the role of BIN1 in AD. The Specific Aims of this proposal are: Aim 1: To test the hypothesis that BIN1 cellular expression and localization are altered in AD brain. We will investigate the BIN1 expression and alternate splicing in normal and diseased human brain. We will determine the subcellular localization of BIN1 by fractionation and confocal microscopy, and clarify the ultrastructural BIN1 localization using immunoelectron microscopy. Aim 2: To test the hypothesis that downregulation of BIN1 expression will attenuate amyloid and tau pathology in transgenic mice. We will ascertain whether cell-type specific loss of BIN1 expression in neurons or mature oligodendrocytes will attenuate AD-related neuropathology and behavior deficits in transgenic AD mouse models. Aim 3: To test the hypothesis that BIN1 plays a role in oligodendrocyte differentiation, survival, and maturation, as well as myelination in vivo. We will utilize Bin1 cKO mouse models and cultured oligodendrocytes to test this hypothesis. This proposal is timely, unique, and highly innovative. We believe that our investigation will uncover significant insights on BIN1's function in the brain, characterize novel Bin1 cKO mouse models of interest to the AD field, establish whether attenuation of BIN1 expression provides a novel strategy for disease intervention, and lay the foundation for characterization of BIN1 functional variants linked to AD, and guide future functional characterization of biological pathways and pathogenic mechanisms regulated by this major LOAD risk gene.

Lay Summary
Alzheimer's disease (AD) is a devastating age-associated neurodegenerative disorder with no treatment or means that would prevent it, cure it or even slow its progression. BIN1, which encodes an adaptor protein, is one of the recently identified common risk genes within the major susceptibility loci for late-onset Alzheimer's disease. Our investigation will develop novel insights into BIN1 function in oligodendrocytes, and assess, using novel conditional BIN1 knockout mice and transgenic AD mouse models, how diminution of BIN1 expression modifies Alzheimer's disease-related neuropathology and behavior.

Further information available at:

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