Exploring the Protective Effect of Myosin 15 in Alzheimer's Disease

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Myosins are cytoskeletal motor proteins that contribute to neuronal function by generating force and modulating actin-based dynamics at the synapse. A recent GWAS study identified a high-confidence, single-nucleotide polymorphism (SNP) in *MYO15A,* encoding the molecular motor myosin 15, that was associated with a significantly reduced risk of developing Alzheimer's Disease (AD). The goal of this study was to explore the function of MYO15A in the brain and how it contributes to the onset of AD pathology. Using *in situ* hybridization, Myo15a transcripts were detected in pyramidal cells of cornu ammonis (CA) regions of the hippocampus in C57/BL6 mouse, in addition to granule cells that project mossy fibers from the dentate gyrus to CA3. Immunofluorescence confirmed these observations and localized endogenous MYO15A protein to synaptic terminals. Mutant *shaker2* mice displayed a statistically impaired recognition of the maze novel arm compared to wild-type littermates, suggesting that MYO15A has a physiological function in learning and memory. Finally, we studied the localization of MYO15A in a mouse model of tauopathy that exhibits cognitive decline and forms pathological neurofibrillary tangles (NFTs). In rTg4510 mice, MYO15A protein was significantly reduced in mossy fibers synapses projecting to CA3, and instead was strikingly accumulated into mature NFTs that co-labeled with hyper-phosphorylated tau protein. Our study reveals a function for MYO15A in hippocampal-dependent learning and memory and uncover a direct association of MYO15A with NFTs, a central neuropathology in AD. Future work is aimed at understanding the function of MYO15A within NFTs and how this can modify disease severity.

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