Lesions containing abnormal aggregated tau protein are one of the diagnostic hallmarks of Alzheimer's disease (AD) and related tauopathy disorders. How aggregated tau leads to the dementia remains enigmatic. We previously identified sut-2 as a gene required for tau neurotoxicity in a transgenic C. elegans model of tauopathy. We demonstrate that overexpression of SUT-2 protein enhances tau induced neuronal dysfunction, neurotoxicity, and accumulation of insoluble tau. We have also explored the relationship between sut-2 and its human homolog, mammalian SUT2 (MSUT2) and find both proteins to be predominantly nuclear and localized to nuclear speckles. Using a cellular model of tauopathy, we demonstrate that neither the localization nor protein levels of MSUT2 change in response to tau. We analyzed MSUT2 protein in age matched post mortem brain samples from AD patients and observe a marked decrease in overall MSUT2 levels in AD relative to controls. Immunohistochemical staining of brain sections show a clear reduction of MSUT2 immunostaining in neurons of AD brain cases relative to controls. RNAi knock down of MSUT2 in cultured human cells overexpressing tau causes a marked decrease in tau aggregation suggesting MSUT2 levels may determine vulnerability to tau toxicity and aggregation. Thus neuroprotective strategies targeting MSUT2 may be of therapeutic significance for tauopathy disorders.