A B-SYNUCLEIN MUTATION LINKED TO FAMILIAL DEMENTIA WITH LEWY BODIES PRODUCES NEURODEGENERATION WHEN EXPRESSED IN MOUSE BRAIN

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Introduction: The discovery of α-synuclein (αS) mutations has made a major contribution to the understanding of the pathogenesis of α-synucleinopathies such as Parkinson's disease and Dementia with Lewy bodies (DLB). In contrast, less attention has been paid to the role of β-synuclein (βS) mutations. Although expression of DLB-linked βS mutants, including P123H and V70M, resulted in lysosomal dysfunction in neuroblastoma cells (Wei et al, J Biol Chem. 2007), it is unclear whether the βS mutations are indeed causative for neurodegeneration in vivo.

Aims: The aim of this study was to characterize the neuropathogenic effect of familial DLB-linked P123H βS in mice brains.

Methods: Transgenic (Tg) mice expressing P123H βS were generated under the Thy-1 promoter. Furthermore, P123H βS mice were crossed with αS mice to generate bigenic mice expressing both P123H βS and αS. After evaluation of various behaviors, mice were subjected to biochemical and histological analyses.

Results: Tg mice expressing P123H βS developed progressive neurodegeneration as characterized by axonal swelling, astrogliosis, and behavioral abnormalities, with memory disorder being more prominent than motor deficits. Furthermore, cross-breeding of P123H βS tg mice with αS tg mice resulted in enhanced neurodegenerative phenotypes.

Conclusions: P123H βS is pathogenic and may cooperate with pathogenic αS to stimulate neurodegeneration in mouse brain, indicating a causative role of P123H βS in familial DLB. Given the neuritic pathology of βS in sporadic α-synucleinopathies, it appears that alteration of βS may contribute to the pathogenesis of a broad range of α-synucleinopathies.