



THE PERRY & RUBY STEVENS

Parkinson's Disease

CENTER OF EXCELLENCE

"Dopaminergic Neuron-Specific Mic60 Deletion Promotes Parkinson's Disease-Like Pathology in Mice"

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Abstract

Background: Mitochondrial dysfunction is a major contributor to Parkinson's disease (PD). Mic60 (Mitofilin), an inner mitochondrial membrane protein essential for cristae organization and mitochondrial function, is reduced in PD brains and experimental models. However, whether Mic60 loss directly contributes to dopaminergic (DA) neuron degeneration *in vivo* remains unknown.

Methods and Results: Using mice with conditional deletion of Mic60 in DA neurons (dMic60^{-/-}), we investigated the consequences of Mic60 deficiency on PD-related pathology and motor function. dMic60^{-/-} mice developed progressive loss of DA neurons, striatal dopamine depletion, α -synuclein aggregation, bradykinesia, and motor dysfunction. These phenotypes were associated with increased mitochondrial dysfunction in the substantia nigra. dMic60^{-/-} mice also exhibited reduced body weight and shortened lifespan. **Conclusion:** DA neuron-specific Mic60 deletion recapitulates key pathological and motor features of PD, demonstrating that Mic60 is critical for maintaining dopaminergic neuronal integrity *in vivo*. These findings identify Mic60 deficiency as a potential mechanism contributing to PD pathogenesis and support the **Mic60 pathway as a potential therapeutic target for PD and other neurodegenerative diseases associated with mitochondrial dysfunction.**