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Altered expression of *CG5961*, a putative *Drosophila melanogaster* homologue of *FBXO9*, provides a new model of Parkinson disease

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ABSTRACT. F-box proteins act as the protein recognition component of the Skp-Cul-F-box class of ubiquitin ligases. Two members of a gene sub-family encoding these proteins, *FBXO7* and *FBXO32*, have been implicated in the onset and progression of degenerative disease. *FBXO7* is responsible for rare genetic forms of Parkinson disease, while *FBXO32* has been implicated in muscle wasting. The third gene in this family, *FBXO9*, is related to growth signaling, but the role of this gene in degenerative disease pathways has not been thoroughly investigated. Characterizing the putative *Drosophila melanogaster* homologue of this gene, *CG5961*, enables modeling and analysis of the consequence of targeted alteration of gene function and the effects on the overall health of the organism. Comparison of the protein domains of *Homo sapiens* FBXO9 and the putative *D. melanogaster* homologue CG5961 revealed a high degree of conservation between the protein domains. Directed expression of *CG5961* (via $CG5961^{EP}$) and inhibition of *CG5961* (through a stable *RNAi* transgene) in the developing *D. melanogaster* eye caused abnormalities in adult structures (ommatidia and inter-ommatidial bristles). Directed expression of either *CG5961*

or *CG5961-RNAi* in the dopaminergic neurons led to a reduced lifespan compared to that in *lacZ* controls. We showed that protein structures of CG5961 and FBXO9 are highly similar and studied the effects of altered expression of *CG5961* in neuron-rich tissues. Our results suggest that *CG5961* activity is necessary for the proper formation of neuronal tissue and that targeted alteration of gene expression in dopaminergic neurons leads to a reduced lifespan.

Key words: *CG5961*; *Drosophila melanogaster*; E3 ubiquitin ligase; *FBXO9*; Neurodegeneration; Parkinson disease

