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BOSTON UNIVERSITY

ANNOUNCEMENT OF FINAL ORAL EXAMINATION

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

CANDIDATE:	**Michael William Nagle**
DEPARTMENT OR PROGRAM:	**Molecular Medicine**
TITLE OF DISSERTATION:	**"The Effect of the Cyclin G-Associated Kinase on the Pathogenesis of Parkinson Disease"**
DATE, TIME, AND PLACE:	**Thursday, April 3, 2014 at 11:00a.m.** **Boston University School of Medicine** **72 E. Concord Street, Room - R115** **Boston, MA 02118**

EXAMINING COMMITTEE

FIRST READER:	**Dr. Richard H. Myers**	
SECOND READER:	**Dr. Chris Pacheco**	
THIRD READER:		
CHAIRMAN OF THE EXAMINING COMMITTEE:	**Dr. Michael Sherman**	**Phone: (617) 638-5971** **Email:sherma1@bu.edu**
ADDITIONAL COMMITTEE MEMBERS:	**Dr. Benjamin Wolozin**	
	Dr. Peter Polgar	

Members of the committee are asked to confirm attendance by replying directly to the Chairman of the Examining Committee.

ALL MEMBERS OF THE SCHOOL OF MEDICINE FACULTY ARE INVITED TO ATTEND.

THE EFFECT OF THE CYCLIN G-ASSOCIATED KINASE ON THE PATHOGENESIS OF PARKINSON DISEASE

MICHAEL WILLIAM NAGLE

Boston University School of Medicine, 2014

Major Professor: Richard H. Myers, Ph.D., Professor of Neurology

ABSTRACT

Parkinson Disease (PD) is the second most common neurodegenerative disorder, clinically characterized by severe motor impairment and pathologically characterized by progressive loss of the dopaminergic neurons of the substantia nigra pars compacta (SNpc) as well as the formation of cellular aggregate deposits called Lewy Bodies. While some advances have been made in understanding the molecular underpinnings of the disorder, the molecular implications of common genetic factors increasing risk for PD have not been adequately studied. First identified by GWA studies in 2009, the *GAK/DGKQ/IDUA* region on chromosome 4p16.3 shows significant genetic association to risk for PD, and the GAK protein has been shown to be associated with the primary component of Lewy Bodies, α-synuclein. In order to determine which gene in the 4p16.3 region may account for the genetic association to PD and to understand the molecular consequences of that association, post-mortem cortical brain tissue from 29 PD and 49 control patients was RNA-sequenced and

differential exon usage in the context of disease and risk variant carrier status was analyzed. Exons in the 3' region of *GAK* were found to be associated to case status, and notably exon 25 expression in *GAK* was associated with both case status and the risk variant. This exon was further observed to be associated to several genes previously shown to interact with *GAK*, including *SNCA*, which codes for α-synuclein. As a proxy for expression of the 3' region of *GAK*, exon 25 was assessed for genome-wide association, and genes showing association to the exon were involved in pathways related to synaptic transmission and neuronal function. In order to validate these findings, microarray analysis of primary rat cortical neurons in which *GAK* expression was reduced by shRNA transduction was performed. *GAK* expression in rat neurons was significantly inversely correlated to endogenous *SNCA* expression, and also exhibited association to pathways involved in synaptic transmission and mitochondrial function. Together, these findings suggest aberrant *GAK* expression related to genetic risk to be an important factor in the pathogenesis of PD through *GAK*'s influence on *SNCA* expression and through dysregulation of important neuronal pathways.