

## Analysis of cellular, transgenic and human models of Huntington's disease reveals tyrosine hydroxylase alterations and substantia nigra neuropathology

George J. Yohrling IV<sup>a,1</sup>, George C.-T. Jiang<sup>b,c</sup>, Molly M. DeJohn<sup>a</sup>, David W. Miller<sup>a</sup>,  
Anne B. Young<sup>a</sup>, Kent E. Vrana<sup>c</sup>, Jang-Ho J. Cha<sup>a,\*</sup>

<sup>a</sup> *Department of Neurology, Center for Aging, Genetics, and Neurodegeneration, Massachusetts General Hospital, 114 16th Street, B114-2000, Charlestown, MA 02129-4404, USA*

<sup>b</sup> *Molecular Genetics Program, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA*

<sup>c</sup> *Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA*

### Abstract

Huntington's disease (HD) is a progressive, autosomal dominant neurodegenerative disorder that is pathologically characterized by a striatal-specific degeneration. Aberrant dopamine neurotransmission has been proposed as a mechanism underlying the movement disorder of HD. We report that the enzymatic activity of tyrosine hydroxylase (TH), the rate-limiting enzyme for dopamine biosynthesis, is decreased in a transgenic mouse model of HD. In addition, mutant huntingtin was found to disrupt transcription of TH and dopamine  $\beta$ -hydroxylase (D $\beta$ H) promoter reporter constructs. In situ hybridization revealed extensive loss of TH mRNA and decreased dopaminergic cell size in human HD substantia nigra. TH-immunoreactive protein was reduced in human grade 4 HD substantia nigra by 32% compared to age-matched controls. These findings implicate abnormalities in dopamine neurotransmission in HD and may provide new insights into targets for pharmacotherapy.