Vps35 D620N knock-in mice display increased susceptibility to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-mediated neurotoxicity

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Vacuolar protein sorting 35 (VPS35) is a core component of the retromer complex required for endosomal membrane-associated protein trafficking. A single missense mutation (D620N) in the VPS35 gene has been associated with late-onset, autosomal dominant familial Parkinson's disease (PD) in both Caucasian and Asian population. Genetic predisposition and environmental factors have long been suspected to contribute to the pathogenesis of PD. To identify the possible interaction between genetic factors and environmental toxins, we investigated whether Vps35 D620N knock-in mice show increased susceptibility to secondary toxic insult of MPTP. We found that MPTP treatment resulted in increased deterioration of the nigrostriatal dopaminergic system as assessed by quantitation of nigral tyrosine hydroxylase (TH) positive neurons and striatal dopamine (DA) levels in Vps35 D620N knock-in mice when compared to non-transgenic littermate controls. In addition, Vps35 D620N knock-in mice showed locomotor dysfunction on exposure of MPTP while control mice did not. These data demonstrated that the Vps35 D620N mutation led to increased vulnerability of dopamine neurons to PD-causing toxins, which confirms that its interaction with environmental factors could contribute to the pathogenesis of PD.