Characterization of the Dnajc13 p.N860S mouse model, a physiological model of alpha-Synuclein overexpression

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DNAJC13/RME-8 is a large, multi-domain molecular co-chaperone that facilitates membrane recycling and cargo sorting of endocytosed proteins. DNAJ proteins contain a central J-domain, which binds and stimulates the ATPase activity of HSC70/HSP70 to facilitate protein folding, degradation, complex assembly or translocation across membranes. In 2014, a c.2564A>G (p.N855S) mutation in DNAJC13 was linked to late-onset autosomal dominant Parkinson's disease in a large multi-incident family. We generated DNAJC13 p.N860S knock-in (DKI) mice, the murine equivalent of the human p.N855S mutation, and characterized their phenotype. We employed a combination of behavioral, biochemical, and imaging techniques including electron microscopy (TEM) on WT and knock-in mice. HPLC and fast-scan cyclic voltammetry were used to interrogate dopaminergic dysfunction associated with Dnajc13 p.N860S while primary neuron culture and alpha-synuclein seeding assays were used to assess the impact of increased alpha-synuclein protein. In the brains of DKI animals, we observe an intact nigrostriatal network, monoamine content and metabolism in the striatum. Basic motor testing reveals a subtle motor phenotype characterized by increased freezing episodes and an inability to complete fine motor tasks when compared to WT littermates. Biochemically, DKI mice have a compromised endo-lysosomal system in turn accelerating the mishandling of alpha-synuclein, a protein implicated in the pathogenesis of PD. DNAJC13 p.N860S knock-in (DKI) mice represent a model of late-onset familial PD through physiological over-expression of alpha-synuclein. Further studies, including the exacerbation of phenotypes with age, are warranted especially to explore the potential effect of DNAJC13 p.N860S on synuclein spreading and dopaminergic cell loss.

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