Cellular and Genetic Mechanisms of Dopamine Transporter-associated Parkinsonism

https://neurodegenerationresearch.eu/survey/cellular-and-genetic-mechanisms-of-dopamine-transporter-associated-parkinsonism/

Principal Investigators

Freja Hansen

Institution

Københavns Universitet

Contact information of lead PI
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Denmark

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Research Abstract

Disturbances in dopaminergic neurotransmission are essential to the pathophysiology of widespread brain disorders such as Parkinson’s disease, ADHD, autism, and addiction. The dopamine transporter (DAT) is a key component in the dopamine system, as it regulates dopamine homeostasis by mediating rapid clearance of dopamine from the synapse. We recently reported that missense mutations in DAT can cause parkinsonism not only in infants, but in adults as well. However, we still have little understanding of the biological processes implicated in the pathophysiology of DAT-associated parkinsonism, and the extent to which these may overlap with the pathophysiology of other Mendelian forms of Parkinson’s disease or

even sporadic Parkinson’s disease. The aim of the present project is to elucidate the pathophysiology of DAT-associated parkinsonism by employment of advanced in vivo and in vitro model systems. I propose a translational approach with the following aims: 1) to systematically characterize a knock-in mouse expressing DAT mutants associated with parkinsonism and evaluate the potential of the mouse as a novel model of Parkinson’s disease; 2) to use guided cellular reprogramming to generate cultures of dopaminergic neurons from skin samples obtained from patients with DAT-associated parkinsonism and thereby identify aberrant disease-relevant cellular phenotypes. I expect these novel model systems to provide new knowledge about processes underlying DAT-associated parkinsonism and to reveal both ‘mutant specific’ and common pathological mechanisms.

Further information available at:

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