Infantile parkinsonism due to dopamine transporter deficiency: functional characterisation and therapeutic approaches .

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Name of Fellow

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Funder

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Contact information of fellow
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Infantile parkinsonism due to dopamine transporter deficiency: functional characterisation and therapeutic approaches .

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Research Abstract
During my PhD, I determined that recessive loss-of-function mutations in the gene encoding the dopamine transporter, DAT (SLC6A3) cause the newly described Dopamine Transporter Deficiency Syndrome (DTDS). DTDS is a severe, progressive, pharmacoresistant early onset movement disorder characterised by dyskinesia, chorea, dystonia, tremor, rigidity and progressive bradykinesia (leading to akinesia). The condition is incurable and trials of all available medical and surgical treatments have not been successful in disease modification. Children with DTDS have a reduced life expectancy (mean age of death 13.6 years). In this proposed research, my key goals are thus to:- 1. Delineate the full extent of the clinical phenotype and genetic mutations identified in DTDS. 2. Further elucidate pathogenic mechanisms in DTDS using a dopaminergic cell disease model. Dopaminergic cells will be differentiated from induced pluripotent stem cells derived from DTDS patient fibroblasts. Dopaminergic ce lls will be characterised using a number of techniques (immunoblotting, immunocytochemistry, HPLC, measurement of tritiated dopamine uptake and amperometry). 3. Develop a gene therapy strategy using the dopaminergic disease model (lentiviral gene transfer) and the DAT knock-out mouse model (AAV9 systemic gene transfer). The effect of gene therapy on both the cell and murine model will be evaluated.

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