Dopamine transporter deficiency syndrome: clinical characteristics, functional insights and novel therapeutic strategies
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Over the last few years, recessive bi-allelic mutations in the gene encoding the dopamine transporter (DAT) have been identified as a cause of infantile parkinsonism-dystonia and juvenile-onset parkinsonism. In the classical form of dopamine transporter deficiency syndrome (DTDS), infants present with an early-onset hyperkinetic disorder with dystonia, chorea and orolingual dyskinesia. During childhood, disease progression leads to a hypokinetic phenotype with parkinsonism. DTDS is associated with significant morbidity and a high risk of mortality in childhood. A wide range of mutations have been reported in DTDS which lead to multifaceted loss of DAT function, including reduced DAT surface membrane expression, abnormal DAT trafficking, impaired protein glycosylation and reduced substrate recognition and transport. We have utilized dopaminergic neurons differentiated from patient-derived pluripotent stem cells to further understand the pathophysiology processes underpinning DTDS, and plan to use this model as a platform for future high throughput drug screening. Furthermore, the use of animal models to elucidate disease mechanisms and assess novel treatment strategies, such as gene therapy, will be discussed.

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