Missense mutations in the dopamine transporter gene: commonality between neuropsychiatric and neurodegenerative diseases?
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Dopamine dysfunction is of central importance in neuropsychiatric diseases, such as schizophrenia, affective disorder, ADHD and autism, as well as in neurodegenerative parkinsonism. The presynaptic dopamine transporter (DAT) mediates reuptake of dopamine and thereby plays a key role in regulating dopamine homeostasis by terminating dopamine signaling and ensuring maintenance of re-usable pools of transmitter. There is accumulating evidence that rare genetic variants in the DAT gene, including de novo mutations, can play a hitherto unknown key role in the pathophysiology of both neuropsychiatric and neurodegenerative disorders. We recently identified two novel DAT coding variants in an adult male diagnosed with both neuropsychiatric disorder and early-onset neurodegenerative parkinsonism. The variants included Ile312Phe in transmembrane segment 6 and a presumed de novo mutant Asp421Asn in the second sodium site. In heterologous cells, both mutants exhibited markedly reduced dopamine uptake capacity but preserved membrane targeting, consistent with impaired catalytic activity. For Asp421Asn, substrate efflux experiments revealed a constitutive, anomalous efflux of dopamine, and electrophysiological analyses identified a cation leak that might contribute to perturbed dopaminergic neurotransmission. To assess causality and investigate disease mechanisms, knock-in mice expressing Asp421Asn and/or Ile312Phe have been generated. Importantly, our genetic screening has led to identification of yet other DAT variants. This includes a variant, located in the C-terminal PDZ binding sequence, which is also associated with neuropsychiatric disorder and early-onset neurodegenerative parkinsonism. In addition, sequencing of 155 patients with severe affective disorder has revealed new variants that currently are subject to phenotypic characterization in vitro. Our data provide strong evidence that missense mutations in DAT can cause or contribute to both neuropsychiatric diseases and movement disorders, and that the resulting disease phenotype depends on the nature of the functional perturbations caused by the mutations. Moreover, the results suggest a yet unappreciated commonality between neurodegenerative and neuropsychiatric diseases and accordingly that the study of DAT missense variants can lead to novel understanding that pertain to dopamine pathologies in general.

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