Dominant negative variant of the dopamine transporter associated with early-onset parkinsonism and psychiatric disease

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The dopamine transporter (DAT) exerts a critical function in dopamine homeostasis by mediating reuptake of dopamine for subsequent storage and release. An increasing number of missense mutations in the dopamine transporter (DAT) have been identified in patients suffering from psychiatric disorders. Moreover, homozygote and compound heterozygote loss-of-function mutations in DAT have been associated with infantile/childhood onset parkinsonism-dystonia. We recently described the first patient, carrying DAT missense mutations, who suffered from both early-onset parkinsonism and ADHD. Here, we further expand the clinical spectrum of DAT-associated disease by presenting an additional patient that presented with the unique combination of early-onset parkinsonism and concurrent psychiatric disorder. This patient is heterozygote for a missense mutation in the C-terminal PDZ-binding domain of DAT. A characterization of the mutant in heterologous cells revealed reduced dopamine uptake capacity (60% of WT DAT), attenuated amphetamine-induced efflux, and slightly reduced expression of DAT-K619N. Strikingly, the mutant exerts a dominant negative effect on WT DAT upon viral expression in mice, seen as a significant reduction in synaptosomal dopamine uptake. Furthermore, two SPECT scans of the patient performed seven years apart, uncovered reduced DAT binding along with a mild progressive worsening during the seven-year period. The identification of yet another patient with DAT-associated parkinsonism and neuropsychiatric disorder further supports that abnormal DAT function may constitute a risk factor for both psychiatric disorders and parkinsonism.

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