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**SNCA Triplication Parkinson's Patient's iPSC-derived DA Neurons Accumulate alpha-Synuclein and Are Susceptible to Oxidative Stress.**

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**Public Summary:**

Parkinson's disease (PD) is an incurable age-related neurodegenerative disorder affecting both the central and peripheral nervous systems. Although common, the etiology of PD remains poorly understood. Genetic studies infer that the disease results from a complex interaction between genetics and environment and there is growing evidence that PD may represent a constellation of diseases with overlapping yet distinct underlying mechanisms. Novel clinical approaches will require a better understanding of the mechanisms at work within an individual as well as methods to identify the specific array of mechanisms that have contributed to the disease. Induced pluripotent stem cell (iPSC) strategies provide an opportunity to directly study the affected neuronal subtypes in a given patient. Here we report the generation of iPSC-derived midbrain dopaminergic neurons from a patient with a triplication in the alpha-synuclein gene (SNCA). We observed that the iPSCs readily differentiated into functional neurons. Importantly, the PD-affected line exhibited disease-related phenotypes in culture: accumulation of alpha-synuclein, inherent overexpression of markers of oxidative stress, and sensitivity to peroxide induced oxidative stress. These findings show that the dominantly-acting PD mutation is intrinsically capable of perturbing normal cell function in culture and confirm that these features reflect, at least in part, a cell autonomous disease process that is independent of exposure to the entire complexity of the diseased brain.

**Scientific Abstract:**

Parkinson's disease (PD) is an incurable age-related neurodegenerative disorder affecting both the central and peripheral nervous systems. Although common, the etiology of PD remains poorly understood. Genetic studies infer that the disease results from a complex interaction between genetics and environment and there is growing evidence that PD may represent a constellation of diseases with overlapping yet distinct underlying mechanisms. Novel clinical approaches will require a better understanding of the mechanisms at work within an individual as well as methods to identify the specific array of mechanisms that have contributed to the disease. Induced pluripotent stem cell (iPSC) strategies provide an opportunity to directly study the affected neuronal subtypes in a given patient. Here we report the generation of iPSC-derived midbrain dopaminergic neurons from a patient with a triplication in the alpha-synuclein gene (SNCA). We observed that the iPSCs readily differentiated into functional neurons. Importantly, the PD-affected line exhibited disease-related phenotypes in culture: accumulation of alpha-synuclein, inherent overexpression of markers of oxidative stress, and sensitivity to peroxide induced oxidative stress. These findings show that the dominantly-acting PD mutation is intrinsically capable of perturbing normal cell function in culture and confirm that these features reflect, at least in part, a cell autonomous disease process that is independent of exposure to the entire complexity of the diseased brain.

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