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**Genetic fine-mapping of the Iowan SNCA gene triplication in a patient with Parkinson's disease.**

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**Public Summary:**

The "Iowa kindred," a large Iowan family with autosomal dominant Parkinson's disease, has been followed clinically since the 1920s at the Mayo Clinic. In 2003, the genetic cause was determined to be a 1.7 Mb triplication of the alpha-synuclein genomic locus. Affected individuals present with an early-onset, severe parkinsonism-dementia syndrome. Here, we present a descendant of the Iowa kindred with novel, disease-associated non-motor findings of reduced heart rate variability, complete anosmia, and a rare skin condition called colloid milium. At autopsy, key neuropathological findings were compatible with diffuse Lewy body disease. Using high-resolution comparative genomic hybridization (CGH) array analysis to fine-map the genomic breakpoints, we observed two independent recombination events of the SNCA locus that resulted in a genomic triplication of twelve genes, including SNCA, and the disruption of two genes, HERC6 and CCSE1, at the genomic breakpoints. In conclusion, we provide further evidence that the mere two-fold overexpression of alpha-synuclein leads to a fulminant alpha-synucleinopathy with rapid progression and severe clinical and neuropathological features.

**Scientific Abstract:**

The "Iowa kindred," a large Iowan family with autosomal-dominant Parkinson's disease, has been followed clinically since the 1920s at the Mayo Clinic. In 2003, the genetic cause was determined to be a 1.7 Mb triplication of the alpha-synuclein genomic locus. Affected individuals present with an early-onset, severe parkinsonism-dementia syndrome. Here, we present a descendant of the Iowa kindred with novel, disease-associated non-motor findings of reduced heart rate variability, complete anosmia, and a rare skin condition called colloid milium. At autopsy, key neuropathological findings were compatible with diffuse Lewy body disease. Using high-resolution comparative genomic hybridization (CGH) array analysis to fine-map the genomic breakpoints, we observed two independent recombination events of the SNCA locus that resulted in a genomic triplication of twelve genes, including SNCA, and the disruption of two genes, HERC6 and CCSE1, at the genomic breakpoints. In conclusion, we provide further evidence that the mere two-fold overexpression of alpha-synuclein leads to a fulminant alpha-synucleinopathy with rapid progression and severe clinical and neuropathological features.

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