



G51D α -synuclein mutation causes a novel Parkinsonian-pyramidal syndrome

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Objective To date, 3 rare missense mutations in the SNCA (α -synuclein) gene and the more frequent duplications or triplications of the wild-type gene are known to cause a broad array of clinical and pathological symptoms in familial Parkinson disease (PD). Here, we describe a French family with a parkinsonian-pyramidal syndrome harboring a novel heterozygous SNCA mutation. Methods Whole exome sequencing of DNA from 3 patients in a 3-generation pedigree was used to identify a new PD-associated mutation in SNCA. Clinical and pathological features of the patients were analyzed. The cytotoxic effects of the mutant and wild-type proteins were assessed by analytical ultracentrifugation, thioflavin T binding, transmission electron microscopy, cell viability assay, and caspase-3 activation. Results We identified a novel SNCA G51D (c.152 G>A) mutation that cosegregated with the disease and was absent from controls. G51D was associated with an unusual PD phenotype characterized by early disease onset, moderate response to levodopa, rapid progression leading to loss of autonomy and death within a few years, marked pyramidal signs including bilateral extensor plantar reflexes, occasionally spasticity, and frequently psychiatric symptoms. Pathological lesions predominated in the basal ganglia and the pyramidal tracts and included fine, diffuse cytoplasmic inclusions containing phospho- α -synuclein in superficial layers of the cerebral cortex, including the entorhinal cortex. Functional studies showed that G51D α -synuclein oligomerizes more slowly and its fibrils are more toxic than those of the wild-type protein. Interpretation We have identified a novel SNCA G51D mutation that causes a form of PD with unusual clinical, neuropathological, and biochemical features.

Résumé en anglais

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