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CHCHD2 and Parkinson's disease

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Funayama and colleagues recently identified a mutation in the *CHCHD2* gene in a large Japanese family with autosomal dominant Parkinson's disease,¹ increasing our knowledge on the monogenic causes of this disorder.^{2,3} They also found the same mutation (182C>T, Thr61Ile) in another family with autosomal dominant Parkinson's disease; the mutation was detected not only in a man with familial disease but also in his brother, who had developed fine tremor at age 10, but had no Parkinsonism at 50 years of age.¹

On the basis of this finding, Funayama and colleagues suggested that a *CHCHD2* mutation might also be the genetic cause in the Arkansas family that we have followed longitudinally and have described previously.⁴ The family is large, with affected individuals in six generations who have clinical parkinsonism, essential tremor, restless legs syndrome, and depression, alone or in various combinations. Signs of postural or action tremor were present in 25 family members, of whom six also had Parkinson's disease. Tremor started insidiously and in three cases during childhood, although it often remained mild.

Neuropathological examination of two family members showed spheroid pigment degeneration with ubiquitin-positive axonal spheroids in the pallidum and substantia nigra, TAR DNA binding protein 43-positive pathology in the basal ganglia, hippocampus, and brainstem, and only sparse Lewy bodies; both individuals had a combination of essential tremor, parkinsonism, and depression.⁴

We identified similar neuropathology in an affected individual from the Swedish family F-081; members of this family had a similar clinical picture to the Arkansas family members. Six members in three generations had Parkinson's disease with an autosomal dominant pattern of inheritance;⁵ symptoms started between ages 55 and 63 years. Three patients with Parkinson's disease had resting tremor, one had severe tremor and received deep brain stimulation, and one had restless legs syndrome for several years before the onset of

parkinsonism. Three patients with parkinsonism had mild cognitive impairment, compared with only one patient in the Arkansas kindred. Neuropathology in one member with tremor-dominant parkinsonism and mild cognitive impairment showed diffuse Lewy body disease and arteriosclerotic vascular disease. Unusually, we found TAR DNA binding protein 43-positive neuronal cytoplasmic and intranuclear inclusions and dystrophic neurites in the hippocampus, but not in the cortex or amygdala, and only sparse lesions in the basal ganglia and brainstem; we did not detect any Alzheimer's pathology.

The entire coding sequence of the **CHCHD2** gene was analysed in four individuals from the Arkansas family, including two with Parkinson's disease and two with essential tremor, and in two first-degree cousins with Parkinson's disease from the Swedish family F-081. The CHCHD2 Thr61Ile substitution was not identified and we did not detect any other mutation in the gene. Although not present in our families, we will be interested to see whether other research on **CHCHD2** mutations will add to the slowly emerging knowledge about the genetics of essential tremor.

Declaration of interests:

The authors declare no competing interests.

Disclosures:

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Authors' contributions:

Andreas Puschmann: Literature search, data collection, data analysis, data interpretation, writing; Dennis W. Dickson: Data collection, data analysis, data interpretation, critical review of manuscript; Elisabet Englund: Data collection, data analysis, data interpretation, critical review of manuscript; Zbigniew K. Wszolek: Study design, data collection, data analysis, data interpretation, critical review of manuscript; Owen A. Ross, PhD: Study design, data collection, data analysis, data interpretation, critical review of manuscript.

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