Partial Trisomy 4q Associated With Young-Onset Dopa-Responsive Parkinsonism

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Objective: To describe a patient who developed a young-onset, dopa-responsive parkinsonism linked to a de novo heterozygous interstitial duplication 4q.

Design: Case report.

Setting: Movement Disorder Outpatient Clinic at the University Hospital Centre, Liège, Belgium.

Patient: A 31-year-old woman.

Main Outcome Measures: Clinical, neuroimaging, and genetic data.

RESULTS: The duplicated region contains 150 known genes, including the α-synuclein (SNCA) gene locus. Motor and 6-[18F]fluoro-L-dopa positron emission tomography features are similar to those previously reported in heterozygote SNCA duplication carriers. Altered expression of other genes contained in the duplicated region may contribute to clinical features that are uncommon in the phenotypic spectrum of SNCA multiplications such as delayed developmental psychomotor milestones during infancy and musculoskeletal abnormalities.

Conclusion: This case report provides new insights on the genetic basis of parkinsonism.

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ANPHA-SYNUCLEIN IS A MAJOR PROTEIN COMPONENT OF LEWY BODIES AND LEWY NEURITES, THE PATHOLOGIC HALLMARKS OF SPORADIC PARKINSON DISEASE (PD). ITS ACCUMULATION IS THOUGHT TO PLAY A MAJOR ROLE IN THE DEGENERATION OF THE SUBSTANTIAL NIGRA PARS COMPACTA DOPAMINERGIC CELLS.1 FURTHERMORE, THE ANALYSES IMPICATING THE α-SYNUCLEIN (SNCA) GENE LOCUS (OMIM 163890) PROVIDE ONE OF THE MOST CONVINCING SETS OF GENETIC ASSOCIATION DATA FOR PD.2 WE REPORT HEREIN CLINICAL, IMAGING, AND GENETIC FINDINGS OF A PATIENT WHO DEVELOPED A YOUNG-ONSET DOPA-RESPONSIVE PARKINSONISM LINKED TO A DE NOVO HETEROZYGOUS INTERSTITIAL Duplication 4q of 41.2 Mb, INCLUDING THE SNCA GENE LOCUS.

Report of a Case

This white female patient, born to non-consanguineous parents, was first examined in our institution at age 2 years because of delayed developmental psychomotor milestones associated with limb hypotonia and poor balance. Her neurological family history was unremarkable. A karyotype analysis revealed a lengthening of the long arm of chromosome 4.3 Findings from the cytogenetic study performed later in her parents and 2 younger brothers were normal.

Her age at acquisition of independent walking was 42 months. Mental retardation became rapidly obvious, and she needed special education in school until the age of 21 years. She developed left-hand dominance for cartoon coloring but was never able to write or read.

She was reexamined in our institution at age 31 years because of a 1-year history of progressive loss of function of her left arm. Her parents also reported motor slowing, a left-hand rest tremor, and left-foot torsion during walking. Clinical examination mainly revealed moderate left-dominant, akinetorigid, and tremulous parkinsonism, along with a mild ataxic gait. She also presented with additional features, including distal limb amyotrophy, slight nocturia, moderate dorsal and lumbar scoliosis, and twelfth paired ribs hypoplasia. Mental retardation was obvious: her spoken language was poor, and her total IQ score on the Wechsler Adult Intelligence Scale was below 43. Findings from detailed neuropsychological testing demonstrated decreased performance for most cognitive functions, including the performance IQ, and a positive association of many subtests with the full-scale IQ score. This patient's progression was severe, with a total IQ score of 0 at age 42 years. Her arm movements became more uncoordinated, with a coarse tremor on the left side of the body. Gait was tortuous during walking. The right arm became flexed and pronated, and the right foot showed tonic contractions. She walked with a left-footed, left-hand resting tremor and an advocate hand posture (Fig 1).

Her speech was impaired, and she was completely unable to write or read. Her trunk showed movement slowing, a left-hand rest tremor, and left-arm fusclee gait. Her parents also reported motor slowing, a left-hand rest tremor, and left-foot torsion during walking. Clinical examination mainly revealed moderate left-dominant, akinetorigid, and tremulous parkinsonism, along with a mild ataxic gait. She also presented with additional features, including distal limb amyotrophy, slight nocturia, moderate dorsal and lumbar scoliosis, and twelfth paired ribs hypoplasia. Mental retardation was obvious: her spoken language was poor, and her total IQ score on the Wechsler Adult Intelligence Scale was below 43. Findings from detailed neuropsychological testing demonstrated decreased performance for most cognitive functions,
including visuospatial tasks, mental calculation, executive functions, and short-term and long-term verbal memory.

Magnetic resonance imaging workup showed hydrocephalus (Evans index = 0.4) without transependymal edema and a slight upper dorsal hydromyelia. These abnormalities were unchanged at imaging follow-up. Cerebral perfusion studies with technetium Tc 99m ethyl cysteinate dimer single-photon emission tomography (PET) revealed a mild bilateral parietooccipital defect. The investigation of striatal dopaminergic terminals with 6-[18F]fluoro-L-Dopa (18F-dopa) PET demonstrated a bilateral and severe decrease of tracer uptake (Figure 1).

The patient was started on L-dopa therapy and dopamine agonists, which were very successful in improving motor parkinsonian features. Several weeks after the initiation of dopatherapy, the patient developed mild to moderate motor fluctuations and dyskinesia. Dopaminergic agonists were not well tolerated and increased dyskinesia. At follow-up by one of us (D.D.) 9 years after diagnosis, there was no impression of further progressive cognitive decline while the beneficial effect of the dopamnergic therapy on motor symptoms was maintained (her Hoehn and Yahr score while taking medication was 3 on a 5-point scale; her total daily L-dopa equivalent dose at her last visit was 516 mg) despite a very narrow therapeutic window between bradykinesia and dyskinesia (her score on Unified Parkinson Disease Rating Scale motor subsection 4 was 10).

A multiplex, ligation-dependent probe amplification of exons 1, 3, 4, 5, and 6 demonstrated a heterozygous duplication at the SNCA gene locus. The total size of the duplicated region on chromosome 4, estimated from a comparative genomic hybridization array analysis, was 41.2 MB and extended from 4q21.23 to band 4q28.1 (Figure 2).

### Figure 1
6-[18F]fluoro-L-Dopa (18F-dopa) positron emission tomographic (PET) scan. 18F-dopa PET axial images at the level of dorsal (A) and ventral striatum (B) illustrating a severe reduction of tracer uptake in the dorsal striatum bilaterally. Striatal-occipital ratio values are as follows: posterior putamen: left, 1.45; right, 1.65; anterior putamen: left, 1.65; right, 1.64; head of caudate: left, 1.83; right, 2.04. Although parkinsonian signs clearly predominated on the left side of the body, there was no convincing asymmetry in putaminal 18F-dopa uptake. This pattern is similar to what has been previously reported using 123I-fluoropropyl-carbomethoxy-3β-iodophenyltropane (FP-CIT) single-photon emission tomography (DaTSCAN) or 18F-dopa PET in SNCA duplication families. This contrasts with the asymmetrical caudorostral gradient in striatal dopaminergic terminals loss seen in most patients with apparently sporadic Parkinson disease.

### Figure 2
Genetic data. A, The patient’s karyotype (G-banding). The arrow points to the duplicated region on the abnormal chromosome 4. B, Comparative genomic hybridization array analysis. Upper area of black and green dots along horizontal line: an average ratio of 0 (black spots) represents a normal number of chromosome region copies (2). An average ratio of 0.5 (green spots) indicates the excess of 1 chromosome region copy (3 copies instead of 2). Thick horizontal gray bar at the bottom: different bands on chromosome 4. The number of megabases indicates the relative position and size of each band from the p telomere to the q telomere. The comparison between the upper and lower areas indicates a duplication of 41.2 MB of the region of chromosome 4 from band 4q21.2 to band 4q28.

### COMMENT
Our patient, who carries 3 copies of the SNCA gene, developed motor and 18F-dopa PET features similar to those previously reported in heterozygote SNCA duplication carriers in both families with autosomal dominant parkinsonisms and apparently sporadic PD cases.5,6 The early age at onset of motor disturbances and the early development of drug-related motor complications observed in our patient have been previously reported in SNCA duplication carriers.5,6 Besides parkinsonism, this patient has not (yet) developed other features reported in some SNCA duplication carriers, such as myoclonus or severe dystonia.3,11

Nevertheless, the data presented herein do not prove that the clinical and imaging phenotypes of parkinsonism are causally related to the heterozygote SNCA duplication. The overproduction of α-synuclein in individuals harboring more than 2 copies of the SNCA gene is considered to be the primary cause of excessive accumulation of Lewy bodies and Lewy neurites in neural cells,
but SNCA gene expression was not measured in this case. Among other possible diagnoses, dopa-responsive dystonia (DRD) is unlikely on the basis of clinical and \(^{18}\)F-dopa PET findings. L-dopa–induced dyskinesia is uncommon in DRD, and existing reports failed to demonstrate such a severe reduction in striatal \(^{18}\)F-dopa uptake.\(^{12}\) In DRD, \(^{18}\)F-dopa uptake in the striatum was found to be either unchanged\(^{12}\) or slightly reduced.\(^{13}\) We did not test for Gaucher disease, which can cause dopa-responsive parkinsonism,\(^{14}\) but the patient’s family history is negative for that disease, and to date she does not present any other features supporting this diagnosis.

The present case differs from previously reported cases in several respects. First, the cytogenetic findings were first published in 1974;\(^{9}\) this is possibly one of the first descriptions of partial trisomy 4q. Second, this patient has a de novo SNCA duplication, whereas with a few exceptions most previous cases were familial.\(^{9,9}\) Third, the size of the duplicated region is about 1 order of magnitude larger than ever reported in SNCA duplications associated with dopa-responsive parkinsonism.\(^{15,16}\) The duplicated region contains 150 known genes (a table listing the 150 putative genes contained in the duplicated region is available at the authors’ website: http://www.movere.org). Of note, a mutation in 1 of these genes, which encodes 1 member of the alcohol dehydrogenase family (ADHIC [OMIM 103730]), has been previously associated with parkinsonism.\(^{17}\) Altered expression of other genes in the duplicated region may have contributed to clinical features that are uncommon in the phenotypic spectrum of SNCA multiplications, such as delayed developmental psychomotor milestones during infancy, ataxic gait, and musculoskeletal abnormalities. These features overlap with those previously reported in partial trisomy 4q syndrome that involved a similar genetic region.\(^{18,19}\) However, parkinsonism was not described in those pediatric cases.

Further clinical follow-up of this patient will increase knowledge of the phenotypic heterogeneity of SNCA duplication carriers and should help to better clarify the pathophysiological characteristics of PD.

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