

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

Gaëtan Garraux, MD, PhD; Jean-Hubert Caberg, PhD; Jean-François Vanbellinghen, MSc; Mauricette Jamar, MD; Vincent Bours, MD, PhD; Gustave Moonen, MD, PhD; Dominique Dive, MD, PhD

**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  $\alpha$ -synuclein (*SNCA*) gene locus. Motor and 6- $^{18}\text{F}$ 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.

*Arch Neurol.* 2012;69(3):398-400

**A**LPHA-SYNUCLEIN IS A MAJOR proteic 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.<sup>1</sup> Furthermore, the analyses implicating the  $\alpha$ -synuclein (*SNCA*) gene locus (OMIM 163890) provide one of the most convincing sets of genetic association data for PD.<sup>2</sup> 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 lengthen-

ing of the long arm of chromosome 4.<sup>3</sup> 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, akineto-rigid, 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 45. Findings from detailed neuropsychological testing demonstrated decreased performance for most cognitive functions,

**Author Affiliations:** Le Fonds de la Recherche Scientifique, Brussels, Belgium (Dr Garraux); MOVERE Group (Dr Garraux) and Departments of Neurology (Drs Garraux, Moonen, and Dive) and Human Genetics (Drs Caberg, Jamar, and Bours and Mr Vanbellinghen), University Hospital Center, Liège, Belgium; and MOVERE Group, Cyclotron Research Center, University of Liège, (Dr Garraux), Liège. Mr Vanbellinghen is now with the Department of Molecular Biology, Institut de Pathologie et de Génétique ASBL, Gosselies, Belgium.

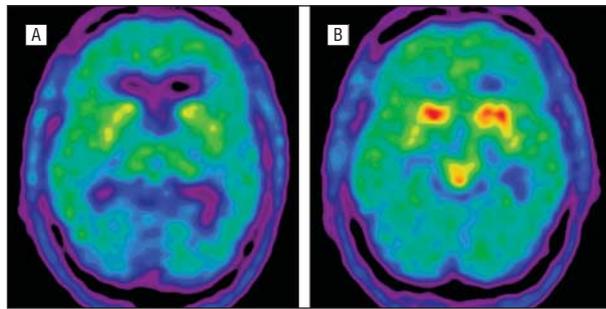
including visuospatial tasks, mental calculation, executive functions, and short-term and long-term verbal memory.

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 studied 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-[<sup>18</sup>F]fluoro-L-dopa (<sup>18</sup>F-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 dopaminergic 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 band 4q21.23 to band 4q28.1 (**Figure 2**).

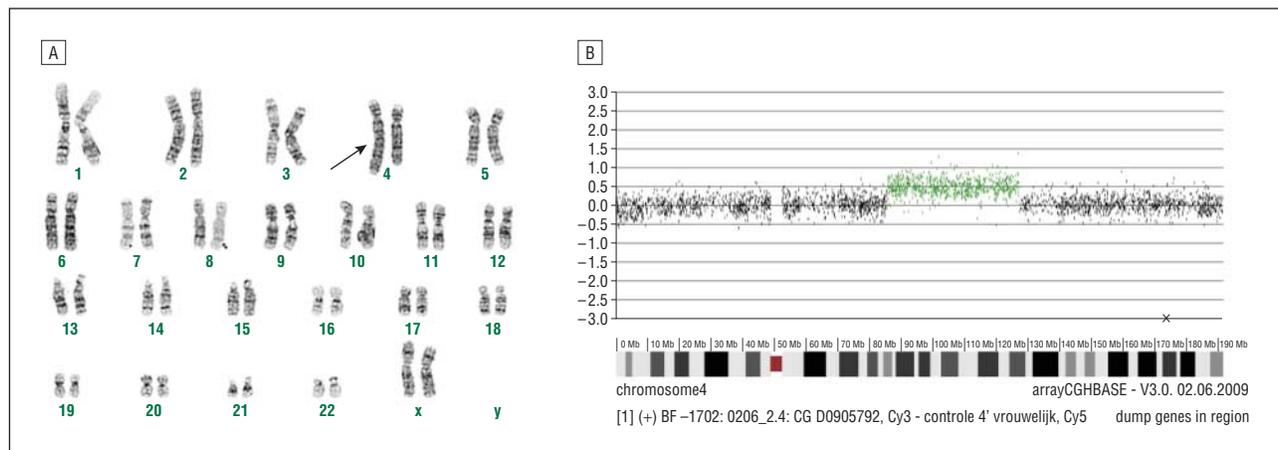


**Figure 1.** 6-[<sup>18</sup>F]fluoro-L-dopa (<sup>18</sup>F-dopa) positron emission tomographic (PET) scan. <sup>18</sup>F-dopa PET axial images at the level of dorsal (A) and ventral striatum (B) illustrating a severe reduction of tracer uptake in the dorsal striatum bilaterally. Striatal-occipital 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 <sup>18</sup>F-dopa uptake. This pattern is similar to what has been previously reported using <sup>123</sup>I-fluoropropyl-carbomethoxy-3β-4-iodophenyltropane (FP-CIT) single-photon emission tomography (DaTSCAN) or <sup>18</sup>F-dopa PET in *SNCA* multiplication families.<sup>4,5</sup> This contrasts with the asymmetrical caudorostral gradient in striatal dopaminergic terminals loss seen in most patients with apparently sporadic Parkinson disease.<sup>6</sup>

## COMMENT

Our patient, who carries 3 copies of the *SNCA* gene, developed motor and <sup>18</sup>F-dopa PET features similar to those previously reported in heterozygote *SNCA* duplication carriers in both families with autosomal dominant parkinsonism<sup>7</sup> and apparently sporadic PD cases.<sup>5,8</sup> 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.<sup>9,10</sup> Besides parkinsonism, this patient has not (yet) developed other features reported in some *SNCA* duplication carriers, such as myoclonus or severe dysautonomia.<sup>11</sup>

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,



**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.

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 <sup>18</sup>F-dopa PET findings. L-dopa-induced dyskinesia is uncommon in DRD, and existing reports failed to demonstrate such a severe reduction in striatal <sup>18</sup>F-dopa uptake.<sup>12</sup> In DRD, <sup>18</sup>F-dopa uptake in the striatum was found to be either unchanged<sup>12</sup> or slightly reduced.<sup>13</sup> We did not test for Gaucher disease, which can cause dopa-responsive parkinsonism,<sup>14</sup> 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<sup>3</sup>; 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.<sup>5,8</sup> 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.<sup>15,16</sup> 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 (*ADH1C* [OMIM 103730]), has been previously associated with parkinsonism.<sup>17</sup> 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.<sup>18,19</sup> 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 pathophysiologic characteristics of PD.

**Accepted for Publication:** June 27, 2011.

**Correspondence:** Gaëtan Garraux, MD, PhD, MOVERE Group, Department of Neurology, University Hospital Center of Liège, and Cyclotron Research Center, University of Liège, 4000 Liège, Belgium (ggarraux@ulg.ac.be).

**Author Contributions:** *Study concept and design:* Garraux and Dive. *Acquisition of data:* Vanbellinghen, Jamar, and Dive. *Analysis and interpretation of data:* Garraux, Caberg, Vanbellinghen, Bours, Moonen, and Dive. *Drafting of the manuscript:* Garraux Caberg. *Critical revision of the manuscript for important intellectual content:* Garraux, Vanbellinghen, Jamar, Bours, Moonen, and Dive.

**Administrative, technical, and material support:** Garraux, Vanbellinghen, and Dive. **Study supervision:** Garraux, Bours, Moonen, and Dive.

**Financial Disclosure:** None reported.

**Additional Contributions:** The comparative genomic hybridization array analysis was performed by Bjorn Menten, DrIr, Center for Medical Genetics, University Hospital of Ghent, Belgium.

## REFERENCES

1. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. *Nature*. 1997;388(6645):839-840.
2. Nalls MA, Plagnol V, Hernandez DG, et al; International Parkinson Disease Genetics Consortium. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet*. 2011;377(9766):641-649.
3. Herman B, Distèche C, Ghymers D, Frederic J. Un cas d'allongement des bras longs d'un chromosome B4 par insertion [46XX:ins. (4?)(q23?)]. *Hum Genet*. 1974;22(3):255-260.
4. Muenter MD, Forno LS, Hornykiewicz O, et al. Hereditary form of parkinsonism:dementia. *Ann Neurol*. 1998;43(6):768-781.
5. Ahn TB, Kim SY, Kim JY, et al. Alpha-Synuclein gene duplication is present in sporadic Parkinson disease. *Neurology*. 2008;70(1):43-49.
6. Brooks DJ, Ibanez V, Sawle GV, et al. Differing patterns of striatal <sup>18</sup>F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Ann Neurol*. 1990;28(4):547-555.
7. Chartier-Harlin MC, Kachergus J, Roumier C, et al. Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. *Lancet*. 2004;364(9440):1167-1169.
8. Nishioka K, Ross OA, Ishii K, et al. Expanding the clinical phenotype of SNCA duplication carriers. *Mov Disord*. 2009;24(12):1811-1819.
9. Bruggemann N, Odin P, Gruenewald A, et al. Re: Alpha-synuclein gene duplication is present in sporadic Parkinson disease. *Neurology*. 2008;71(16):1294.
10. Sironi F, Trotta L, Antonini A, et al. Alpha-Synuclein multiplication analysis in Italian familial Parkinson disease. *Parkinsonism Relat Disord*. 2010;16(3):228-231.
11. Puschmann A, Wszolek ZK, Farrer M, Gustafson L, Widner H, Nilsson C. Alpha-synuclein multiplications with parkinsonism, dementia or progressive myoclonus? *Parkinsonism Relat Disord*. 2009;15(5):390-392.
12. Nygaard TG, Takahashi H, Heiman GA, Snow BJ, Fahn S, Calne DB. Long-term treatment response and fluorodopa positron emission tomographic scanning of parkinsonism in a family with dopa-responsive dystonia. *Ann Neurol*. 1992;32(5):603-608.
13. Sawle GV, Leenders KL, Brooks DJ, et al. Dopa-responsive dystonia: [18F]dopa positron emission tomography. *Ann Neurol*. 1991;30(1):24-30.
14. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N Engl J Med*. 2009;361(17):1651-1661.
15. Ross OA, Braithwaite AT, Skipper LM, et al. Genomic investigation of alpha-synuclein multiplication and parkinsonism. *Ann Neurol*. 2008;63(6):743-750.
16. Ibañez P, Lesage S, Janin S, et al; French Parkinson's Disease Genetics Study Group. Alpha-synuclein gene rearrangements in dominantly inherited parkinsonism: frequency, phenotype, and mechanisms. *Arch Neurol*. 2009;66(1):102-108.
17. Buervenich S, Carmine A, Galter D, et al. A rare truncating mutation in *ADH1C* (G78Stop) shows significant association with Parkinson disease in a large international sample. *Arch Neurol*. 2005;62(1):74-78.
18. Jeziorowska A, Ciesla W, Houck GE Jr, et al. Cytogenetic and molecular identification of a de novo direct duplication of the long arm of chromosome 4(q21.3->q31.3). *Am J Med Genet*. 1993;46(1):83-87.
19. Navarro EG, Romero MC, Expósito IL, et al. De novo interstitial tandem duplication of chromosome 4(q21-q28). *Am J Med Genet*. 1996;62(3):297-299.