and p.A53T families. We were not able to perform mutation segregation analysis with disease but nonetheless postulate that *SNCA* p.H50Q is a novel cause of parkinsonism and dementia in this kindred. ■

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Alpha-Synuclein Gene Duplication: Marked Intrafamilial Variability in Two Novel Pedigrees

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ABSTRACT

Background: Multiplications of the *SNCA* gene that encodes alpha-synuclein are a rare cause of autosomal dominant Parkinson's disease (PD).

Methods: Here, we describe 2 novel families in which there is autosomal dominant PD associated with *SNCA* duplication, and we compare the clinical features of all known patients carrying 3 or 4 *SNCA* copies.

Results: Affected members in family A presented with early onset PD that was variably associated with nonmotor features, such as dysautonomia, cognitive deficits, and psychiatric disturbances. In family B, the clinical presentation ranged from early onset PD-dementia with psychiatric disturbances to late onset PD with mild cognitive impairment.

Conclusions: The presence of 4 *SNCA* copies is associated with a rich phenotype, characterized by earlier onset of motor and nonmotor features compared with patients who bear 3 *SNCA* copies. The clinical spectrum associated with *SNCA* duplications is wide, even within a single family, suggesting a role for as yet unidentified genetic or environmental modifiers. © 2013 *Movement* Disorder Society

Key Words: Parkinson's disease; SNCA; alpha-synuclein; gene duplication; deep brain stimulation

Alpha-synuclein represents the most abundant protein of Lewy bodies, the typical cytoplasmic inclusions found in Parkinson's disease (PD), Lewy body dementia, and other disorders known as synucleinopathies.[1] Missense mutations or multiplications of the *SNCA* gene, which encodes alpha-synuclein, represent a rare cause of autosomal dominant PD.[2–6] It is interesting to note that *SNCA* triplications are known to cause a homogeneous phenotype of early onset PD with dementia and other nonmotor features, whereas

Additional Supporting Information may be found in the online version of this article.

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SNCA duplications are associated with a much wider clinical spectrum.[7–10]

We report 2 novel, unrelated families with PD caused by *SNCA* duplications that were characterized by marked intrafamilial variability. We illustrate the clinical picture in 4 patients and provide a statistical comparison of patients bearing 3 or 4 *SNCA* copies.

Case Reports

Family A

Patient A-II:1

The proband is a man aged 56 years who was born in Northern Argentina to nonconsanguineous parents. Parkinsonian signs started at age 43 years with resting tremor of the right upper limb. He was treated first with pergolide (0.5 mg 4 times daily [QID]) and selegiline (5 mg daily), then with levodopa (L-dopa) (50 mg QID).

Four years after onset, he presented a typical parkinsonian picture with right-side prevalence and excellent response to treatment. Urinary urgency and constipation were reported. Brain magnetic resonance imaging revealed mild brain atrophy. Motor complications started 6 years after onset, with predictable wearing off and early morning painful dystonia in the left foot.

Fourteen years after onset, he had motor fluctuations but no peak-dose dyskinesias. In the OFF condition, he presented axial dystonia with trunk bending to the right side (Pisa syndrome) and frequent freezing episodes. Nonmotor symptoms consisted of visual hallucinations, depression, and mild orthostatic dizziness due to postural hypotension. Three years later, nonmotor features were severe, with urinary retention and frank dementia. He had also developed dysphagia that required endoscopic gastrostomy. Motor axonal polyneuropathy with lower limb prevalence also was detected.

Patient A-II:2

The proband's sister had onset at 44 years with left leg tremor. One year later, she presented a severe rapid eye movement behavioral sleep disorder, and L-dopa (50 mg QID) was started with appreciable improvement. Two years after onset, she developed early motor complications with motor fluctuations and peak-dose dyskinesias. Later, she gradually experienced nonmotor symptoms, consisting of visual and acoustic hallucinations and autonomic features, such as constipation, urinary urgency with occasional retention, and orthostatic hypotension. At age 51 years, her score on the Mini-Mental State Examination (MMSE) was 26.3 of 30. She received bilateral subthalamic deep brain stimulation (DBS) implants, which greatly improved her motor condition. At age 54 years, her United Parkinson's Disease Rating Scale score had improved by 42% compared with the preimplant condition, her preoperative L-dopa equivalent daily dose had been reduced by 58%, but her MMSE score had worsened to 23.2 of 30.

Family B

Patient B-III:2

The proband is a man aged 44 years who was born to nonconsanguineous Italian parents. During his childhood, he presented symptoms suggestive of attention deficit hyperactivity disorder. He soon became addicted to several substances of abuse and was reported as hyperactive and a risk-seeker. Parkinsonian signs had started at age 32 years with hypomimia, depressive symptoms, and global slowness. He received ropinirole, with motor benefit; however, 4 years later, he developed compulsive intake of high doses of ropinirole, leading to atrial fibrillation. Seven years after onset, the patient complained of postural instability and was put on L-dopa treatment (100 mg QID), with modest motor improvement and the appearance of motor fluctuations. Over the next 2 years, he progressively developed cognitive deficit (MMSE score, 18 of 30) and worsening of psychiatric symptoms, with visual and auditory hallucinations, delusions, and physical aggressiveness.

Patient B-II:2

The proband's 78-year-old mother did not report any neurological symptoms; however, on examination, she presented with mild parkinsonian signs characterized by hypomimia, diffuse rigidity, and bradykinesia. Her cognitive performance also was impaired (MMSE score, 22 of 30; Montreal Cognitive Assessment [MoCA] score, 17 of 30).

Genetic Analysis

Multiplex ligation-dependent probe analysis detected a heterozygous duplication of all *SNCA* exons in all tested patients. Quantitative real-time polymerase chain reaction analysis confirmed the *SNCA* duplication, which was not detected in the healthy sister of the family B proband.

Duplication of the genomic region encompassing *SNCA* was further characterized in patients A-II:2, B-II:2, and B-III:2 using high-resolution single nucleotide polymorphism-array analysis. In family A, the duplicated segment at the 4q21 locus spanned 773 Kb and included the entire *SNCA* and *MMRN1* genes and the first 3 exons of the *KIAA1680* gene. In both members of family B, the duplicated region was much larger, spanning 4820 Kb and including *SNCA* and additional 24 neighboring genes (Fig. 1). In an attempt to explain the phenotypic differences observed in family B, we compared genotypes in patients B-II:2 and B-III:2 for

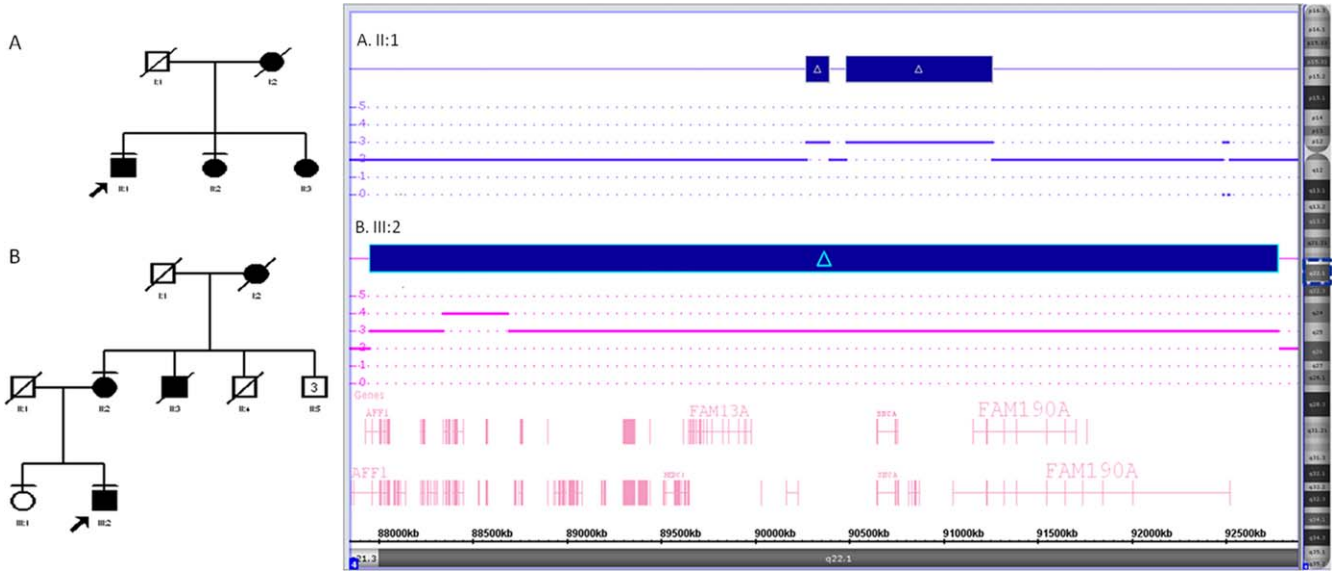

FIG. 1. (**A**) Simplified pedigrees of families A and B are illustrated. Black symbols denote affected individuals. Dead members are marked with a diagonal bar; a horizontal bar above symbols denotes individuals who were examined clinically and underwent genetic testing. Arrows indicate the probands. (**B**) A single nucleotide polymorphism array output (Affymetrix, High Wycombe, Buckinghamshire, United Kingdom) for (**top**) patient AII:2 and (**bottom**) and patient BIII:2 reveals the extension of the chromosome 4q duplicated region. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the *SNCA* REP1 microsatellite (an upstream, polymorphic microsatellite of the SNCA gene) and 6 single nucleotide polymorphisms known as PD risk factors, but we failed to detect any genotypic differences between the proband and his mother.

Phenotypic Comparison

With this study, the number of reported families carrying *SNCA* multiplications is raised to 34, including 28 families with duplications and 6 families with triplications. Eighteen probands had a positive familial history and 15 were sporadic (see Supplementary Table 1).

A comparison of the individuals who carried 3 or 4 *SNCA* copies is summarized in Table 1. Age at disease onset was clustered in the third to fifth decades in carriers of 4 *SNCA* copies, whereas it spanned the fourth to the eighth decades in patients who had duplications, with a peak in the fifth decade (see Supplementary Fig. 1). The presence of 4 *SNCA* copies is associated with a fully penetrant PD phenotype, nearly invariably accompanied by autonomic, psychiatric, and cognitive symptoms (range, 85%–100% of carriers). Conversely, the phenotype in patients with *SNCA* duplications is more variable, with the occurrence of isolated nonmotor features in approximately 50% in carriers and in up to 30% of nonpenetrant, healthy carriers.

Discussion

The main phenotype in these families was characterized by early onset PD with variable degrees of cognitive impairment, psychiatric disturbance, and autonomic dysfunction. These findings are in line with recent reports of early onset PD-dementia in patients carrying 3 *SNCA* copies[7,8,11,12] and argue against the

TABLE 1. Phenotypic expression in carriers of 3 or 4 alpha-synuclein gene copies

Variable	Three SNCA copies	Four SNCA copies
Subjects	73	28
No. of patients/no. with genetic testing	53/40	28/14[a]
No. of asymptomatic carriers	20	0
Age at onset: Mean ± SD [range], y	49.9 ± 11.8 [30–77]	36.8 ± 9.4 [24–60][b]
Reported follow-up: Mean ± SD [range], y	10.4 ± 6 [1–25]	9.2 ± 5.9 [1–22]
Autonomic dysfunction		
No. of patients/total no. with available data (%)	14/34 (41.2)	14/15 (93.3)[b]
Age at onset: Mean ± SD [range], y	51.9 ± 10.3 [41–71]	36.3 ± 8.4 [25–49][b]
Psychiatric disturbances		
No. of patients/total no. with available data (%)	25/41 (61)	8/9 (88.8)
Age at onset: Mean ± SD [range], y	52.6 ± 11.6 [34–74]	42.0 ± 6.3 [34–50][c]
Cognitive impairment		
No. of patients/total no. with available data (%)	25/47 (52.3)	25/27 (92.6)[b]
Age at onset: Mean ± SD [range], y	57.4 ± 11.6 [38–77]	43.4 ± 11.0 [25–58][b]

[a]Two patients had SNCA homozygous duplication.
[b]$P \leq 0.001$.
[c]$P = 0.04$;
SNCA, alpha-synuclein gene; SD, standard deviation.

paradigm that *SNCA* duplications are invariably associated with a more benign parkinsonian phenotype that is indistinguishable from late onset, idiopathic PD.[13,14]

Intra-familial variability was observed especially in family B. The proband (B-III:2) presented a phenotype resembling that associated with *SNCA* triplication, with early onset, severe parkinsonism and prominent nonmotor features. Conversely, his mother (B-II:2) had only mild parkinsonian signs of which she was unaware. The proband also presented a drug addiction/risk-taking behavior, as previously reported in the Iowa kindred, characterized by *SNCA* triplication,[15] suggesting a role for SNCA in regulating dopamine release, as demonstrated previously in mouse models.[16]

Phenotypic variability is a feature of *SNCA* duplications, ranging from asymptomatic carrier status,[7,9,17,18] to late onset PD,[13,14] to earlier onset presentations that include prominent nonmotor features.[7–9,11,12,17,19] The presence of 4 *SNCA* copies is associated with early onset PD with prominent nonmotor features, as reported in most studies.[12,17,20–22]

We performed an analysis between individual patients rather than between family means, because the reported families have a significant degree of intrafamilial phenotypic heterogeneity. Their broad phenotype is reported in Supplementary Table 1.

A possible correlation between clinical presentation and the extension of the deletion has been ruled out, because similar phenotypes have been observed in patients carrying duplications of the *SNCA* gene only as well as duplications of large regions that include up to 33 distinct genes.[17] Indeed, we also failed to detect a correlation between the extension of the rearrangement and the clinical presentation of the disease in our 2 families. A possible explanation is that, in patients with 3 *SNCA* copies, other genetic modifier factors and/or environmental triggers may influence the penetrance and expression of the disease.[7,9] In patients B-III:2 and B-II:2, despite the striking difference in phenotype severity, we failed to detect genotypic differences in several polymorphisms known to be associated to PD risk; however, the potential involvement of other still unknown variants lying within or outside the duplicated region cannot be ruled out.

Subthalamic DBS is not the strategy of choice for treating patients who have *SNCA* multiplications because of the frequent occurrence of early cognitive impairment, which represents a contraindication to DBS surgery. To date, only 2 *SNCA*-duplicated patients have been reported who underwent subthalamic DBS with good motor response but developed subsequent cognitive impairment (both with short follow-up).[7,23] In line with these cases, our patient A-II:2 had relevant motor improvement up to 3 years after surgery, but then developed cognitive impairment.

The 2 families described here confirm the importance of performing *SNCA* gene dosage analysis in patients who have autosomal dominant PD, early onset, and prominent nonmotor features, such as autonomic dysfunction, psychiatric disturbances, and dementia. In patients who carry an *SNCA* duplication, subthalamic DBS can be effective to treat motor complications, providing a satisfactory, long-term outcome, although it may expedite the manifestation of cognitive impairment.

Legend to the Video

Segment 1. Patient II-1 of family A (proband) has parkinsonian signs characterized by hypomimia and bradykinesia, which is more pronounced on the left side. In addition, he presents axial dystonia with trunk bending to the right side (Pisa syndrome) and freezing episodes.

Segment 2. Patient II-2, the proband's sister, received bilateral subthalamic deep brain stimulation (DBS) implant about 2 years before the videotape. Myerson's sign is present. She has left-prevalent bradykinesia accompanied by mild axial dystonia with trunk bending to the left side (Pisa syndrome) and no freezing or postural instability.

Segment 3. Patient III-2 of family B (proband) is demented, withdrawn, and presents a symmetric parkinsonian picture characterized by severe akinesia, rigidity, stooped posture with slight antecollis, and lateral trunk flexion. In addition, small-stepped gait and increased blink rate also are evident.

Segment 4. Patient II-2 of family B (the proband's mother) has parkinsonian signs characterized by hypomimia, diffuse rigidity, and bradykinesia of the upper and lower limbs, which is more pronounced on the left side.

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Long-Term Safety and Efficacy of Preladenant in Subjects With Fluctuating Parkinson's Disease

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ABSTRACT

Background: Preladenant is a selective adenosine A_{2A} receptor antagonist under investigation for Parkinson's disease treatment.

Methods: A phase 2 36-week open-label follow-up of a double-blind study using preladenant 5 mg twice a day as a levodopa adjunct in 140 subjects with fluctuating Parkinson's disease was conducted. The primary end point was adverse event (AE) assessment. Secondary (efficacy) analyses included hours/day spent in OFF and ON states and dyskinesia prevalence/severity.

Results: The 36-week open-label phase was completed by 106 of 140 subjects (76%). AE-related treatment discontinuations occurred in 19 subjects (14%). Treatment-emergent AEs, reported by $\geq$15% of subjects, were dyskinesia (33%) and constipation (19%). Preladenant 5 mg twice a day provided OFF time reductions (1.4–1.9 hours/day) and ON time increases (1.2–1.5 hours/day) throughout the 36-week treatment relative to the baseline of the double-blind study.

Conclusions: Long-term preladenant treatment (5 mg twice a day) was generally well tolerated and provided sustained OFF time reductions and ON time increases.

Key Words: adenosine A_{2A} receptor antagonist; Parkinson's disease; fluctuations; OFF timeclinical trial

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