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Autosomal dominant Parkinson's disease caused by *SNCA* duplications

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Abstract

The discovery in 1997 that mutations in the *SNCA* gene cause Parkinson's disease (PD) greatly advanced our understanding of this illness. There are pathogenic missense mutations and multiplication mutations in *SNCA*. Thus, not only a mutant protein, but also an increased dose of wild-type protein can produce autosomal dominant parkinsonism. We review the literature on *SNCA* duplications and focus on pathologically-confirmed cases. We also report a newly-identified American family with *SNCA* duplication whose proband was autopsied. We found that over half of the reported cases with *SNCA* duplication had early-onset parkinsonism and non-motor features, such as dysautonomia, rapid eye movement sleep behavior disorder (RBD), hallucinations (usually visual) and cognitive deficits leading to dementia. Only a few cases have presented with typical features of PD. Our case presented with depression and RBD that preceded parkinsonism, and dysautonomia that led to an initial diagnosis of multiple system atrophy. Dementia and visual hallucinations followed. Our patient and the other reported cases with *SNCA* duplications had widespread cortical Lewy pathology. Neuronal loss in the hippocampal cornu ammonis 2/3 regions were seen in about half of the autopsied *SNCA* duplication cases. Similar pathology was also observed in *SNCA* missense mutation and triplication carriers.

Keywords

Parkinson's disease; alpha-synuclein; *SNCA*; duplication; pathology

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Introduction

Approximately 10% of patients with Parkinson's disease (PD) report a positive family history [1]. Twenty-one PARK loci have been identified for familial PD, including autosomal dominant, autosomal recessive, and X-linked forms, and causative genes have been discovered for a majority of them [2]. Mutations in six genes (*SNCA*, *LRRK2*, *EIF4G1*, *VPS35*, *DNAJC13* and *CHCHD2*) were reported to cause autosomal dominant PD. The pathogenicity of *SNCA*, *LRRK2* and *VPS35* mutations is established beyond a doubt from many observations, even though the penetrance of some of the mutations in these genes is incomplete [3]. The pathogenic effect of some of the mutations in the more recently identified other PD genes awaits confirmation.

The first missense *SNCA* mutation causing PD, p.Ala53Thr, was discovered in 1997 [4]. Currently, six other known missense mutations (p.Ala18Thr, p.Ala29Ser, p.Ala30Pro, p.Glu46Lys, p.His50Gln and p.Gly51Asp [5]) and gene multiplications (genomic duplications and triplications) have been reported in *SNCA*.

In this review, we focus on reports of patients with *SNCA* duplication mutations that were examined neuropathologically. We also report a new American family with *SNCA* duplication, presenting an additional neuropathology of a carrier of this mutation. Given the central role of alpha-synuclein in many patients with parkinsonism, we consider these rare patients very informative for the study of clinical and pathological aspects of alpha-synuclein overabundance.

Review of *SNCA* duplication cases

We retrieved publications containing clinical or pathological reports on carriers of *SNCA* duplication from systematic searches in public databases and the authors' own literature collections. Forty-six cases from 31 families with *SNCA* duplication have been reported. The families were found with a wide geographical distribution (Europe, Asia, and North and South America), but nearly one-third of the reported families were of Japanese origin. There were 19 families with an autosomal dominant inheritance, 10 sporadic cases, and two consanguineous families.

The mean age of onset in 44 patients with heterozygous *SNCA* duplication was 48 years (SD: 13 years, range 18–77 years). Some patients showed typical PD phenotypes, but atypical or more severe clinical courses were often reported. Cognitive deficits, depression, hallucinations, rapid eye movement sleep behavior disorder (RBD), and dysautonomia were described in many patients. Table 1 displays the frequencies of these non-motor symptoms in the 44 cases. Hallucinations were the only feature present significantly more often than not (χ^2 test, $p < 0.01$) in these patients. However, the data on these non-motor features was not available for some cases, and disease duration differed widely between the patients reported. In general, the non-motor phenotypes of these cases resembled the phenotypes frequently seen in dementia with Lewy bodies (DLB), with prominent cognitive and psychiatric impairments and RBD.

About half of the patients with *SNCA* duplication developed motor complications, such as wearing off and dyskinesia, early in the disease course. The mean duration from disease onset to the development of motor complications was four years (n=15, SD: 3 years, range 1–12 years). Three cases underwent bilateral subthalamic nuclei deep brain stimulation (DBS) with good results on motor symptoms [6–8]. Two of them did not show any significant cognitive decline after DBS surgery with one year and four years follow-up respectively [6, 7]. The third case developed dementia after DBS procedure [8]. Thus, DBS might be potentially useful for selected *SNCA* duplication patients who have severe motor complications but do not have any cognitive deficits.

One affected member of each of the two consanguineous families with *SNCA* duplications, one Japanese and one Pakistani, was homozygous for *SNCA* duplication and thus possessed four copies of *SNCA*, resembling the situation in *SNCA* triplication carriers [9, 10]. Symptoms manifested at 28 years in the Japanese patient with four *SNCA* copies, versus at 57 (mean, n=3, SD: 16, range 39–71) years in family members with three copies [9]. Similarly, the homozygous duplication carrier from Pakistan developed symptoms at the age of 31 years; whereas her mother, carrying *SNCA* duplication, remained clinically unaffected when examined at the age of 72 years [10]. In both homozygous duplication cases the phenotypes were characterized by early-onset and rapidly-progressive parkinsonism followed by dementia, which has been seen in the *SNCA* triplication cases [11].

Genetic analyses have revealed widely variable sizes of the duplicated genomic region, ranging from 0.2 to 41.2 Mb and containing anywhere from 2 to 150 genes [11–13]. Combined with haplotype analyses, this data indicates there is no common ancestor but duplications have arisen independently in most of the families reported [12]. The fact that sporadic cases and asymptomatic carriers have been found indicates that the penetrance is incomplete and likely age-dependent. There are reports of two patients whose parents were healthy and were not carriers of *SNCA* duplication. Thus these two patients had a *de novo* mutation [13, 14]. There is no clear correlation between the size of the duplication and resulting clinical phenotypes, implying that other genetic and environmental factors may contribute.

Interestingly, it is known that a Swedish family with *SNCA* duplication and a Swedish American family with triplication were descended from a common ancestor [15]. Genetic analysis of this large pedigree indicates a duplication event occurred at first through recombination, and subsequently triplication was generated by unequal crossing-over [15]. This result suggests a possible conversion to triplication could occur in the future generations of duplication families.

Neuropathology of *SNCA* duplication patients

Neuropathological examinations were conducted on four Japanese patients and one British patient with *SNCA* duplication (Table 2) [9, 16–21]. Three of the Japanese cases (II-4, III-1, IV-1) were from the same family. The mean age of onset in all five patients was 51 (SD 14, range 38–71) years, and the mean disease duration was 12 (SD 5, range 7–20) years. Four of these manifested parkinsonism as their initial symptom and subsequently developed

dementia and hallucinations. The British case presented with hallucinations that began in childhood; this patient also suffered from anxiety and panic disorder that began at age eight years. The parkinsonism associated with this case appeared at age 38 years [21].

All five cases showed typical symptoms of classic PD with asymmetry and a good initial response to levodopa treatment. However, the effects of levodopa diminished as the disease progressed. Two of the cases exhibited wearing off and dyskinesia. Dementia was found in all five cases 5 years (SD 5, range: 0–13) after the onset of parkinsonism. Dysautonomia and abnormal behavior were described in four of the cases, and RBD was described in two. Other symptoms such as gaze palsy, myoclonus, blepharospasm, dystonia, and frontal lobe release signs were seen in various combinations in all five cases. In a single patient who subsequently was examined post mortem, 99m-TcECD single-photon emission computed tomography scan demonstrated hypoperfusion in the frontotemporal and occipital lobes. This patient also had MIBG myocardial scintigraphy that showed a reduced H/M ratio, indicating cardiac sympathetic denervation [19].

All *SNCA* duplication cases shared similar neuropathological findings. There was marked depigmentation and neuronal loss in the substantia nigra and locus ceruleus, neuronal loss in the basal nucleus of Meynert and the dorsal motor nucleus of the vagus nerve, widespread Lewy bodies (LBs) from the brainstem to the neocortex [22], and Lewy neurites in the cornu ammonis (CA) 2/3 region, originally reported as a distinct pathologic signature of diffuse Lewy body disease [23]. These findings in the duplication cases correspond to a pathological diagnosis of high likelihood DLB [24]. In addition, the neuronal loss in the CA2/3 region was observed in two cases, which is typical of *SNCA* mutation carriers [25, 26] and distinct from neuronal loss in CA1, which is usually associated with TDP-43 pathology [26, 27]. These two cases also showed neuronal loss in the amygdala. Alpha-synuclein-positive glial inclusions were seen in all five cases, which is typical of *SNCA* mutation carriers [28]. Pathology in epicardial autonomic nerves was observed in three cases [29]. In four cases, only a few neurofibrillary tangles were detected in the transentorhinal cortex, corresponding to Braak stage I–II, whereas in one case, a carrier of a homozygous *apolipoprotein-ε4*, there was extended tangle pathology as in Braak stage III.

New family with *SNCA* duplication

Our index case was a 43-year-old, left-handed American man who experienced nightmares, moved violently, screamed, and even walked while asleep, and had excessive daytime sleepiness. He also complained of depression. Sleep apnea and RBD were diagnosed at the time. Two years later he developed mild memory problems and occasional urinary urgency. No parkinsonian signs were detected on the neurological examination. Neuropsychological examination was normal. Thus his complaints were attributed to depressive mood and sleep disturbances. About a year later, he insidiously developed left hand tremor, cramps in his left leg, soft voice, and episodes of dizziness and even fainting. By age 53 years, there was action tremor, bradykinesia, decreased arm swing, facial masking, foot dystonia, square-wave jerks, and severe dysautonomia, including orthostatic hypotension with fainting, urinary incontinence, constipation, and erectile dysfunction. Treatment with carbidopa/levodopa partially improved his motor symptoms. He was diagnosed as having multiple

system atrophy (MSA) based on the presence of prominent dysautonomia. Magnetic resonance imaging of his brain was normal. Subsequently, cognitive decline became clinically evident and motor functions gradually worsened. At age 60 years, the patient was unable to perform daily motor tasks without assistance. Mini Mental State Examination score was 20 out of 30 points at age 61 years. The clinical diagnosis was changed to DLB because his cognitive state fluctuated. He also developed episodic confusion and visual hallucinations, especially after sundown. Confusion and hallucinations worsened when he used higher doses of carbidopa/levodopa. He also showed palilalia, frontal lobe release signs, abulia, and Capgrass syndrome. He died at age 63 years, about 15 years after the onset of his parkinsonism.

A postmortem examination showed severe neuronal loss in the substantia nigra, the locus ceruleus, the dorsal motor nucleus of the vagus, and the basal nucleus of Meynert with LBs and Lewy neurites (Fig. 1a–e, m). There was severe neuronal loss in the amygdala and the hippocampus, and the latter was associated with neuronal loss and gliosis in the CA2/3 region, but the neurons were preserved in the CA1 region (Fig. 1f–h). LBs and Lewy neurites were also evident in the CA2/3 region (Fig. 1i). Spongiform change was observed in temporal cortex (Fig. 1j). Lewy pathology extended to widespread areas of the cortex, and this was consistent with diffuse neocortical DLB (Fig. 1k, l). There were a few alpha-synuclein-positive glial cytoplasmic inclusions in the white matter of the basal ganglia (Fig. 1n). There were only a few neurofibrillary tangles in the transentorhinal cortex, consistent with Braak stage 0 to I. Because of this characteristic pathological pattern, including hippocampal CA2/3 neuronal loss [25], we conducted a genetic analysis to search for an *SNCA* mutation and confirmed the presence of an *SNCA* duplication mutation.

The proband's three children currently remain asymptomatic, and the oldest child is now 45 years old, which is still below the median age of onset of 47 years as calculated in our review. Genetic counselling is made difficult by the wide range of ages at which symptoms develop in *SNCA* duplication carriers, and by the fact that penetrance remains incomplete even at 79 years of age [20]. Additionally, the proband's mother died at the age of 66 years. She was diagnosed as having Alzheimer's disease in her mid to late 50s. The medical records available to us indicate that she had muscle rigidity. Thus, we presume she carried *SNCA* duplication; however, an autopsy and genetic analysis were not performed. The family tree is presented in Fig. 1.

Conclusions

SNCA duplication carriers can present with a relatively early onset of parkinsonism and considerable non-motor symptoms. The clinical phenotype often includes elements typical of other synucleinopathies such as MSA [15] or, more frequently, DLB. The fact that all pathologically confirmed cases, including our case, showed diffuse neocortical LBs with minimal Alzheimer type pathology indicates the high likelihood of DLB. At this juncture, still too few families and affected patients who have come to postmortem neuropathologic examination have been described, so drawing precise clinical-pathological correlations is difficult. Future descriptions of additional families with *SNCA* multiplications may facilitate these correlations. With next-generation molecular genetic testing, including whole genome

sequencing, entering routine clinical practice, it is quite possible that such patients will be more easily identified.

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References

1. Spatola M, Wider C. Genetics of Parkinson's disease: the yield. *Parkinsonism Relat Disord*. 2014; 20(Suppl 1):S35–S38. [PubMed: 24262184]
2. Puschmann A. Monogenic Parkinson's disease and parkinsonism: Clinical phenotypes and frequencies of known mutations. *Parkinsonism Relat Disord*. 2013; 19:407–415. [PubMed: 23462481]
3. Sharma M, Ioannidis JP, Aasly JO, Annesi G, Brice A, Bertram L, Bozi M, Barcikowska M, Crosiers D, Clarke CE, Facheris MF, Farrer M, Garraux G, Gispert S, Auburger G, Vilariño-Güell C, Hadjigeorgiou GM, Hicks AA, Hattori N, Jeon BS, Jamrozik Z, Krygowska-Wajs A, Lesage S, Lill CM, Lin JJ, Lynch T, Lichtner P, Lang AE, Libioulle C, Murata M, Mok V, Jasinska-Myga B, Mellick GD, Morrison KE, Meitinger T, Zimprich A, Opala G, Pramstaller PP, Pichler I, Park SS, Quattrone A, Rogaeva E, Ross OA, Stefanis L, Stockton JD, Satake W, Silburn PA, Strom TM, Theuns J, Tan EK, Toda T, Tomiyama H, Uitti RJ, Van Broeckhoven C, Wirdefeldt K, Wszolek Z, Xiromerisiou G, Yomono HS, Yueh KC, Zhao Y, Gasser T, Maraganore D, Krüger R. GEOPD consortium. A multi-centre clinico-genetic analysis of the VPS35 gene in Parkinson disease indicates reduced penetrance for disease-associated variants. *J Med Genet*. 2012; 49:721–726. [PubMed: 23125461]
4. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science*. 1997; 276:2045–2047. [PubMed: 9197268]
5. Fujioka S, Ogaki K, Tacik PM, Uitti RJ, Ross OA, Wszolek ZK. Update on novel familial forms of Parkinson's disease and multiple system atrophy. *Parkinsonism Relat Disord*. 2014; 20(Suppl 1):S29–S34. [PubMed: 24262183]
6. Antonini A, Pilleri M, Padoan A, Landi A, Ferla S, Biundo R, D'Avella D. Successful subthalamic stimulation in genetic Parkinson's disease caused by duplication of the α -synuclein gene. *J Neurol*. 2012; 259:165–167. [PubMed: 21761143]
7. Shimo Y, Natori S, Oyama G, Nakajima M, Ishii H, Arai H, Hattori N. Subthalamic deep brain stimulation for a Parkinson's disease patient with duplication of SNCA. *Neuromodulation*. 2014; 17:102–103. [PubMed: 23441980]
8. Ahn TB, Kim SY, Kim JY, Park SS, Lee DS, Min HJ, Kim YK, Kim SE, Kim JM, Kim HJ, Cho J, Jeon BS. alpha-Synuclein gene duplication is present in sporadic Parkinson disease. *Neurology*. 2008; 70:43–49. [PubMed: 17625105]
9. Ikeuchi T, Kakita A, Shiga A, Kasuga K, Kaneko H, Tan CF, Idezuka J, Wakabayashi K, Onodera O, Iwatsubo T, Nishizawa M, Takahashi H, Ishikawa A. Patients homozygous and heterozygous for

- SNCA duplication in a family with parkinsonism and dementia. *Arch Neurol*. 2008; 65:514–519. [PubMed: 18413475]
10. Kojovic M, Sheerin UM, Rubio-Agusti I, Saha A, Bras J, Gibbons V, Palmer R, Houlden H, Hardy J, Wood NW, Bhatia KP. Young-onset parkinsonism due to homozygous duplication of α -synuclein in a consanguineous family. *Mov Disord*. 2012; 27:1827–1829. [PubMed: 23283657]
 11. Ross OA, Braithwaite AT, Skipper LM, Kachergus J, Hulihan MM, Middleton FA, Nishioka K, Fuchs J, Gasser T, Maraganore DM, Adler CH, Larvor L, Chartier-Harlin MC, Nilsson C, Langston JW, Gwinn K, Hattori N, Farrer MJ. Genomic investigation of alpha-synuclein multiplication and parkinsonism. *Ann Neurol*. 2008; 63:743–750. [PubMed: 18571778]
 12. Ibáñez P, Lesage S, Janin S, Lohmann E, Durif F, Destée A, Bonnet AM, Brefel-Courbon C, Heath S, Zelenika D, Agid Y, Dürr A, Brice A. French Parkinson's Disease Genetics Study Group. Alpha-synuclein gene rearrangements in dominantly inherited parkinsonism: frequency, phenotype, and mechanisms. *Arch Neurol*. 2009; 66:102–108. [PubMed: 19139307]
 13. Garraux G, Caberg JH, Vanbellinghen JF, Jamar M, Bours V, Moonen G, Dive D. Partial trisomy 4q associated with young-onset dopa-responsive parkinsonism. *Arch Neurol*. 2012; 69:398–400. [PubMed: 22410449]
 14. Brueggemann N, Odin P, Gruenewald A, Tadic V, Hagenah J, Seidel G, Lohmann K, Klein C, Djarmati A. Re: Alpha-synuclein gene duplication is present in sporadic Parkinson disease. *Neurology*. 2008; 71:1294. [PubMed: 18852448]
 15. Fuchs J, Nilsson C, Kachergus J, Munz M, Larsson EM, Schüle B, Langston JW, Middleton FA, Ross OA, Hulihan M, Gasser T, Farrer MJ. Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. *Neurology*. 2007; 68:916–922. [PubMed: 17251522]
 16. Ishikawa A, Takahashi H, Tanaka H, Hayashi T, Tsuji S. Clinical features of familial diffuse Lewy body disease. *Eur Neurol*. 1997; 38(Suppl 1):34–38. [PubMed: 9276199]
 17. Wakabayashi K, Hayashi S, Ishikawa A, Hayashi T, Okuizumi K, Tanaka H, Tsuji S, Takahashi H. Autosomal dominant diffuse Lewy body disease. *Acta Neuropathol*. 1998; 96:207–210. [PubMed: 9705138]
 18. Nishioka K, Hayashi S, Farrer MJ, Singleton AB, Yoshino H, Imai H, Kitami T, Sato K, Kuroda R, Tomiyama H, Mizoguchi K, Murata M, Toda T, Imoto I, Inazawa J, Mizuno Y, Hattori N. Clinical heterogeneity of alpha-synuclein gene duplication in Parkinson's disease. *Ann Neurol*. 2006; 59:298–309. [PubMed: 16358335]
 19. Obi T, Nishioka K, Ross OA, Terada T, Yamazaki K, Sugiura A, Takanashi M, Mizoguchi K, Mori H, Mizuno Y, Hattori N. Clinicopathologic study of a SNCA gene duplication patient with Parkinson disease and dementia. *Neurology*. 2008; 70:238–241. [PubMed: 18195271]
 20. Nishioka K, Ross OA, Ishii K, Kachergus JM, Ishiwata K, Kitagawa M, Kono S, Obi T, Mizoguchi K, Inoue Y, Imai H, Takanashi M, Mizuno Y, Farrer MJ, Hattori N. Expanding the clinical phenotype of SNCA duplication carriers. *Mov Disord*. 2009; 24:1811–1819. [PubMed: 19562770]
 21. Kara E, Kiely AP, Proukakis C, Giffin N, Love S, Hehir J, Rantell K, Pandraud A, Hernandez DG, Nacheva E, Pittman AM, Nalls MA, Singleton AB, Revesz T, Bhatia KP, Quinn N, Hardy J, Holton JL, Houlden H. A 6.4 Mb duplication of the α -synuclein locus causing frontotemporal dementia and Parkinsonism: phenotype-genotype correlations. *JAMA Neurol*. 2014; 71:1162–1171. [PubMed: 25003242]
 22. Pouloupoulos M, Levy OA, Alcalay RN. The neuropathology of genetic Parkinson's disease. *Mov Disord*. 2012; 27:831–842. [PubMed: 22451330]
 23. Dickson DW, Ruan D, Crystal H, Mark MH, Davies P, Kress Y, Yen SH. Hippocampal degeneration differentiates diffuse Lewy body disease (DLBD) from Alzheimer's disease: light and electron microscopic immunocytochemistry of CA2-3 neurites specific to DLBD. *Neurology*. 1991; 41:1402–1409. [PubMed: 1653914]
 24. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Lodos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M. Consortium on DLB. Diagnosis and management of

- dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005; 65:1863–1872. [PubMed: 16237129]
25. Farrer M, Kachergus J, Forno L, Lincoln S, Wang DS, Hulihan M, Maraganore D, Gwinn-Hardy K, Wszolek Z, Dickson D, Langston JW. Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. *Ann Neurol*. 2004; 55:174–179. [PubMed: 14755720]
26. Markopoulou K, Dickson DW, McComb RD, Wszolek ZK, Katechlidou L, Avery L, Stansbury MS, Chase BA. Clinical, neuropathological and genotypic variability in SNCA A53T familial Parkinson's disease. Variability in familial Parkinson's disease. *Acta Neuropathol*. 2008; 116:25–35. [PubMed: 18389263]
27. Aoki N, Murray ME, Ogaki K, Fujioka S, Rutherford NJ, Rademakers R, Ross OA, Dickson DW. Hippocampal sclerosis in Lewy body disease is a TDP-43 proteinopathy similar to FTLT-TDP Type A. *Acta Neuropathol*. 2015; 129:53–64. [PubMed: 25367383]
28. Fujishiro H, Imamura AY, Lin WL, Uchikado H, Mark MH, Golbe LI, Markopoulou K, Wszolek ZK, Dickson DW. Diversity of pathological features other than Lewy bodies in familial Parkinson's disease due to SNCA mutations. *Am J Neurodegener Dis*. 2013; 2:266–275. [PubMed: 24319644]
29. Orimo S, Uchihara T, Nakamura A, Mori F, Ikeuchi T, Onodera O, Nishizawa M, Ishikawa A, Kakita A, Wakabayashi K, Takahashi H. Cardiac sympathetic denervation in Parkinson's disease linked to SNCA duplication. *Acta Neuropathol*. 2008; 116:575–577. [PubMed: 18751989]

Figure 1.

Neuropathological findings of the proband (a–n) and a pedigree of newly identified American family with *SNCA* duplication (o). Macroscopic features in midbrain, pontomesencephalic junction and rostral pons. Almost complete loss of neuromelanin pigment in substantia nigra (arrows) (a). Lewy bodies (LBs) in the substantia nigra (b, c) and the locus ceruleus (d, e). Neuronal loss in hippocampal cornu ammonis 3 (CA3) denoted by asterisk (f), preservation of neurons in cornu ammonis 1 (CA1) (g), neuronal loss and gliosis in CA3 (h) and Lewy neurites in CA3 with alpha-synuclein immunohistochemistry (i).

Spongiform change (j), and cortical LBs and Lewy neurites in temporal cortex (k). LBs and Lewy neurites in the amygdala (l). Intra-axonal LBs in the dorsal motor nucleus of vagus (m). Glial cytoplasmic inclusions (arrowheads) in white matter, and Lewy dots and threads in gray matter in the basal ganglia (n). H&E staining (b, d, f–h and j) and alpha-synuclein immunohistochemistry (c, e, i, and k–n). Scale bars indicate 1 cm (a), 20 μ m (b–e, k, m and n), 500 μ m (f) and 50 μ m (g–j and l). Standard pedigree symbols are used; arrow, the proband; circles, female; squares, male; diamonds, obscured gender to protect privacy; slush through symbols, diseased individuals; solid symbol, affected individual; gray symbol, diagnosed with Alzheimer's disease (o).

Table 1

Non-motor characteristics of cases with *SNCA* duplication mutation

Symptoms	Number of cases			p-value ^b	
	Positive	Negative	Not reported		
Cognitive deficits	24	20	0	44	0.55
Depression	13	7	24	44	0.18
Hallucinations ^a	21	6	17	44	0.004
RBD	7	5	32	44	0.56
Dysautonomia	15	9	20	44	0.22

RBD, rapid eye movement sleep behavior disorder

^a types of hallucination; visual, n=16; auditory, n=4; olfactory, n=2

^b comparison between positive and negative cases by χ^2 test

Table 2
Clinical and pathological features of the autopsy cases with *SNCA* duplication mutation

References Cases	II-4	[9, 16, 17] III-1	IV-1	[18–20] B-1	[21] III-3	Our case
Ethnicity	Japanese	Japanese	Japanese	Japanese	British	American
Sex	Male	Female	Male	Male	Female	Male
Age at onset (y)	71	61	39	47	38	late 40's
Age at death (y)	78	70	54	67	49	63
Disease duration (onset to death) (y)	7	9	15	20	11	about 15
Initial symptom	gait disturbance, hand tremor	gait disturbance, left hand tremor	gait disturbance	clumsiness of left hand	right arm tremor	left hand tremor
Motor symptoms						
Tremor	+	+	+	+	+	+
Rigidity	+	+	+	+	+	+
Bradykinesia	+	+	+	+	+	+
Postural instability	+	+	+	–	+	+
Asymmetry	NA	+	+	+	+	+
Levodopa response	+	+	+	+	+	dyskinesia
Motor complications	–	wearing off, dyskinesia	wearing off, dyskinesia	NA	NA	dyskinesia
Non-motor symptoms						
Dysautonomia	+	+	+	NA	+	+
Depression	NA	NA	NA	–	– ^a	+
Dementia (age at onset, y)	+(73)	+(65)	+(46)	+(60)	+(38)	+(61)
Hallucination	+	+	+	+	+ ^a	+
Abnormal behavior	NA	+	+	+	+	+
RBD	NA	NA	NA	+	+	+
Other findings	gaze palsy, myoclonus	gaze palsy, myoclonus	gaze palsy	fluctuation of consciousness, hypophonic dysarthria, dysphagia	blepharospasm, dystonic neck, hypometric saccades, frontal release signs	square wave jerks, foot dystonia, frontal release signs, abulia,

References Cases	II-4	[9, 16, 17] III-1	IV-1	[18–20] B-1	[21] III-3	Our case
						palatalia, cerebellar dysfunction
Pathology						
Diagnosis	DLB (diffuse neocortical)	DLB (diffuse neocortical)	DLB (diffuse neocortical)	DLB (diffuse neocortical)	DLB (diffuse neocortical)	DLB (diffuse neocortical)
Findings in CA2/3 area	Lewy neurites	Lewy neurites	Neuronal loss and Lewy neurites	Neuronal loss and Lewy neurites	Lewy neurites	Neuronal loss and Lewy neurites
Glia1 alpha-synuclein inclusions	+	+	+	+	+	+
Other findings	cardiac sympathetic denervation	cardiac sympathetic denervation	cardiac sympathetic denervation			

CA, cornu ammonis; DLB, dementia with Lewy bodies; NA, not available; RBD, rapid eye movement sleep behavior disorder

^aThis patient suffered from extreme anxiety, panic disorder and hallucination from age 8 years.