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Parkin-related Disease Clinically Diagnosed as a Pallido-Pyramidal Syndrome

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Insights into the etiology of Parkinson's disease (PD) disorders have resulted from the identification of Mendelian genes,¹ including *parkin*. Most patients with *parkin* mutations do not have Lewy body pathology, yet have a clinical syndrome recognized as PD. Here, we describe a man with exceptionally early onset Parkinsonism due to *parkin*.

His symptoms began at the age of 8, with dragging of the left leg, involving the right leg within 6 months, and clawing of the left and then right hand. At the age of 10, he had an asymmetric spastic tetraplegia with lordotic gait, hyperreflexia, and extensor plantar responses. He was suspected to have either a congenital anomaly such as cerebellar ectopia or a high-cervical medullary tumor. He was then noted to have hypomimic facies, generalized cogwheel rigidity, and hyperreflexia. His gait was described as a mixture of step-page and waddle with a tendency to fall backward, walking with extended arms and clawed hands. The diagnosis was revised to a degenerative striatal disorder. Trihexyphenidyl gave considerable benefit. At the age of 13, his diagnosis was juvenile Parkinsonism without known cause. At the age of 17, he had developed a fine postural tremor. At the age of 32, he was noted to have asymmetric rest tremor. He responded very well to an apomorphine challenge.

At the age of 33, when referred to Prof. David Marsden, he had slurred speech, dysphagia, daily falls, and complained of poor memory. He had diminished right arm swing, poor balance on turning with loss of postural reflexes, dystonic posturing of hands and feet, and marked asymmetric bradykinesia (Video, Segment 1). A diagnosis of pallidal atrophy was made, later revised to possible familial pallidal degeneration. Dopamine agonists had some benefit but were poorly tolerated due to confusion and hallucinations. At the age of 36, dysphagia, bladder symptoms, and constipation were attributed to chronic anticholinergic use. He remained cognitively intact but developed depression and anxiety. Thirty-six years after the disease onset, aged 44, he remained independent with intermittent dystonia, mild dysarthria, moderate neck rigidity and asymmetric postural tremor, bradykinesia, and rigidity. His gait showed marked start hesitation with dystonic plantar flexion of the feet, good stride length, and gait freezing. During practically defined off his motor, UPDRS was 68 of 108 (Video, Segment 2). Following 250-mg levodopa, UPDRS improved to 22 of 108 (Video, Segment 3). He underwent bilateral caudal zona incerta deep brain stimulation⁶ at the age of 46 with substantial benefit. Six months postoperatively on stimulator plus oral therapy, the motor UPDRS was 24 of 108 (Video, Segment 4). L-dopa was tried three times during his disease but not tolerated because of dyskinesia. Shortly after his neurosurgery, compound heterozygous *parkin* mutations were identified.

His parents were not consanguineous and neither had neurological symptoms. A maternal aunt was said to have developed stiffness and shuffling gait at the age of 15 but has not been examined. A paternal half-sister was seen at the age of 5 with abnormal gait and left-sided increased tone, but did not develop a progressive movement disorder.

Copy number metrics derived from Illumina Infinium HumanHap550 arrays revealed changes consistent with either homozygous deletion or compound heterozygous deletion at the same locus, within *PRKN*.⁷ Further analysis of the region using multiplex ligation-

dependent probe assay (MLPA, MRC-Holland) confirmed the abnormality and demonstrated a compound heterozygous exon 2/exon 2 1 3 deletion in the *parkin* gene.

Although our patient had an asymmetric L-dopa responsive akinetic-rigid syndrome, meeting the Queen Square Brain Bank criteria for PD, this was considered to be an atypical parkinsonian disorder. The early dysarthria, prominent distal dystonia, and erect posture with flexion of the arms when walking are suggestive of pallidostriatal Parkinsonism-dystonia diseases. Experienced movement disorders experts, before the identification of the *parkin* gene, diagnosed this patient as having pallidal or striatal degeneration. Other notable features of this case include long disease duration, extreme sensitivity to the dyskinesigenic effects of L-dopa, marked problems with gait freezing, and a beneficial response to DBS. The patient sample was included in a screen of young onset PD samples looking for novel gene changes, and we show that the Illumina SNP assay can also be used to identify deletions in genomic DNA. There are relatively few reports of neuropathology in parkin patients.^{9–13} Severe involvement of the substantia nigra and locus coeruleus is common, but other areas of the basal ganglia, including the striatum and pallidum, are usually unaffected. The average onset age in patients with parkin disease is 31 years.¹⁷ Onset before age 10 is rare, and we have only identified six reported cases^{15,18–21} (Table 1). Of those with two identified parkin mutations, all had *parkin* exon 3 deletions. Although relatively common (13% of all mutations²²), we suggest that exon 3 mutations may be particularly likely to be associated with very early onset disease.

LEGENDS TO THE VIDEO

Segment 1 (Aged 35). The patient has bilateral severe bradykinesia for finger taps (slightly worse on the left), with dystonic posturing of the hands. He walks with flexed arms and has gait unsteadiness particularly when turning. He falls and there is an evident marked bilateral dystonic posturing of the feet.

Segment 2 (Aged 45, pre-operative, functionally defined off state). Marked asymmetric bradykinesia is seen and worse on the left. There is gait initiation failure. He walks with flexed arms and has gait freezing.

Segment 3 (Pre operative on state, following L-dopa challenge). Improvement in repeated grips and alternating hand movements.

Segment 4. (Aged 48, post-operative, stimulator on, plus trihexyphenidyl, rasagiline, pramipexole, and amantadine). He has asymmetric bradykinesia with motor arrests while performing finger taps. He takes frequent extra steps when turning, but walks with a good stride length.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Hardy J, Cai H, Cookson MR, Gwinn-Hardy K, Singleton A. Genetics of Parkinson's disease and Parkinsonism. *Ann Neurol* 2006;60:389–398. [PubMed: 17068789]
- Gibb WR, Lees AJ. The significance of the Lewy body in the diagnosis of idiopathic Parkinson's disease. *Neuropathol Appl Neurobiol* 1989;15:27–44. [PubMed: 2542825]
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–184. [PubMed: 1564476]
- Gwinn-Hardy K, Chen JY, Liu HC, et al. Spinocerebellar ataxia type 2 with Parkinsonism in ethnic Chinese. *Neurology* 2000;55: 800–805. [PubMed: 10993999]
- Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-Parkinsonism. *Brain* 2005;128(Part 6):1247–1258. [PubMed: 15788542]
- Plaha P, Ben-Shlomo Y, Patel NK, Gill SS. Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral Parkinsonism. *Brain* 2006;129 (Part 7):1732–1747. [PubMed: 16720681]
- Simon-Sanchez JSS, Matarin M, Fung H-C, et al. Genome-wide SNP assay reveals mutations underlying Parkinson's disease. *Hum Mutat* 2007.
- Jankovic J Searching for a relationship between manganese and welding and Parkinson's disease. *Neurology* 2005;64:2021–2028. [PubMed: 15985567]
- Hayashi S, Wakabayashi K, Ishikawa A, et al. An autopsy case of autosomal-recessive juvenile Parkinsonism with a homozygous exon 4 deletion in the parkin gene. *Mov Disord* 2000;15:884–888. [PubMed: 11009195]
- Farrer M, Chan P, Chen R, et al. Lewy bodies and Parkinsonism in families with parkin mutations. *Ann Neurol* 2001;50:293–300. [PubMed: 11558785]
- van de Warrenburg BP, Lammens M, Lucking CB, et al. Clinical and pathologic abnormalities in a family with Parkinsonism and parkin gene mutations. *Neurology* 2001;56:555–557. [PubMed: 11222808]
- Sasaki S, Shirata A, Yamane K, Iwata M. Parkin-positive autosomal recessive juvenile Parkinsonism with α -synuclein-positive inclusions. *Neurology* 2004;63:678–682. [PubMed: 15326242]
- Pramstaller PP, Schlossmacher MG, Jacques TS, et al. Lewy body Parkinson's disease in a large pedigree with 77 Parkin mutation carriers. *Ann Neurol* 2005;58:411–422. [PubMed: 16130111]
- Kitada T, Asakawa S, Hattori N, et al. Mutations in the parkin gene cause autosomal recessive juvenile Parkinsonism. *Nature* 1998;392:605–608. [PubMed: 9560156]
- Abbas N, Lucking CB, Ricard S, et al. A wide variety of mutations in the Parkin gene are responsible for autosomal recessive Parkinsonism in Europe. French Parkinson's Disease Genetics Study Group and the European Consortium on Genetic Susceptibility in Parkinson's Disease. *Hum Mol Genet* 1999;8:567–574. [PubMed: 10072423]
- Lucking CB, Durr A, Bonifati V, et al. Association between early-onset Parkinson's disease and mutations in the *parkin* gene. *N Engl J Med* 2000;342:1560–1567. [PubMed: 10824074]
- Lohmann E, Periquet M, Bonifati V, et al. How much phenotypic variation can be attributed to *parkin* genotype? *Ann Neurol* 2003;54:176–185. [PubMed: 12891670]
- Periquet M, Latouche M, Lohmann E, et al. Parkin mutations are frequent in patients with isolated early-onset Parkinsonism. *Brain* 2003;126 (Part 6):1271–1278. [PubMed: 12764050]
- Khan NL, Graham E, Critchley P, et al. Parkin disease: a phenotypic study of a large case series. *Brain* 2003;126 (Part 6):1279–1292. [PubMed: 12764051]

20. Poorkaj P, Nutt JG, James D, et al. Parkin mutation analysis in clinic patients with early-onset Parkinson [corrected] disease. *Am J Med Genet A* 2004;129:44–50.
21. Lesage S, Magali P, Lohmann E, et al. Deletion of the *parkin* and PACRG gene promoter in early-onset Parkinsonism. *Hum Mutat* 2007;28:27–32. [PubMed: 17068781]
22. Hedrich K, Eskelson C, Wilmot B, et al. Distribution, type, and origin of *parkin* mutations: review and case studies. *Mov Disord* 2004;19:1146–1157. [PubMed: 15390068]

TABLE 1.

Patients with parkin mutations with age at onset < 10 years

Reference	Age at onset	Mutations	Case ID
15	7	Not specified	–
18	7	Ex 2-4 del/Thr240Met	JMP 37
17	7	Two truncating mutations (location not specified)	–
17	9	At least one missense mutation	–
19	7	(Gly430Asp)/uncharacterized	Case 9
20	8	40bp del Exon 3/del Exon 3	Case C 201
21	8	Del Exon 3/Del PACRG + PRKN Exon 1	Case 431-16
This report	8	Del Exon 2/Del Exon 2+3	–