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Parkinson's disease with Lewy bodies associated with a heterozygous *PARKIN* dosage mutation

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Abstract

Background—*PARKIN* -related disease remains incompletely understood. First, the pathogenicity of heterozygous *PARKIN* mutations is unclear though some evidence supports causality. Second, unlike sporadic Parkinson's disease (PD), Lewy bodies are present only in a minority of cases. Only one other heterozygote *PARKIN* carrier with autopsy findings has been described. Our case adds to the broadening pathological and clinical phenotype of *PARKIN*-related disease.

Methods—Clinical chart, genetic analysis and pathological findings of a patient with familial PD are reviewed.

Results—A 44-year-old man developed slowly progressive tremor-predominant PD with excellent response to levodopa. Genetic analysis revealed a heterozygous *PARKIN* exon 3-4 deletion, also present in two family members with early-onset PD. Post-mortem examination showed severe neuronal loss in the substantia nigra and nucleus coeruleus with presence of diffuse Lewy bodies.

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Conclusions—The deletion is unlikely an incidental finding considering family history, age-at-onset and the presence of clinical and pathological features not typical of sporadic PD.

The role of *PARKIN* heterozygous mutations in the spectrum of disease that spans *PARKIN*-linked parkinsonism (parkin disease) and Parkinson's disease (PD) is not clear. However, some evidence does support the pathogenicity of heterozygous mutations: 1) dosage mutations are more pathogenic than point mutations among heterozygotes;¹ 2) age at onset correlates with number of mutations, even when comparing heterozygotes to controls;² and 3) asymptomatic heterozygous *PARKIN* carriers have abnormal dopaminergic function on F-DOPA PET imaging.³ Heterozygote carriers may be different from carriers of 2 mutations: symptom onset is later (but earlier than sporadic PD), and hyposmia is often present.⁴ Here, we present pathological findings from a heterozygous *PARKIN* exon 3-4 deletion carrier who was evaluated as part of the Consortium on Risk for Early-Onset PD study (CORE-PD).² Only one other heterozygous case with autopsy findings has been described.⁵

A 44-year-old Caucasian man presented with tremor of the right hand. His symptoms progressed slowly, were responsive to trihexyphenidyl, and he did not require levodopa for the first 10 years. He had no dystonia and continued to work until he was 56. At age 66, 22 years after symptom onset, he developed memory loss and hallucinations. At the time, he was taking levodopa (300mg daily), trihexyphenidyl (12mg daily), selegiline and pramipexole (1mg daily). His hallucinations improved partially by discontinuing the pramipexole. Eventually, the trihexyphenidyl was discontinued with some improvement in his memory and confusional episodes. Because of ongoing hallucinations selegiline was also discontinued and quetiapine was initiated (up to 100mg daily), following which the hallucinations resolved. Neuropsychological testing at age 71 confirmed impairments in memory, executive function, visuospatial and language domains consistent with dementia. At the time he was taking levodopa (600mg sustained-release and 150mg immediate release) and quetiapine (100mg daily). The maximum daily levodopa dose reached was 750mg and dyskinesias, which were confined to the face, developed only after 15 years of therapy. He died at age 76.

Dosage analysis performed using semi-quantitative multiplex polymerase chain reaction revealed a heterozygous *PARKIN* exon 3-4 deletion. Point mutations in the *PARKIN* gene were screened by denaturing high performance liquid chromatography (DHPLC) and a custom genotyping array. In addition, full sequencing of *PARKIN* exons and multiplex ligation dependent probe amplification (MPLA) was performed as previously described.⁶ However, we cannot completely rule out additional mutations in *PARKIN* introns. The mutation segregates with disease in this multiplex family: three 2nd degree family members with onset of PD in their 30s had the exon 3-4 deletion plus a 40bp deletion in exon 3 on the other allele (compound heterozygous). Common point mutations in other genes including *SNCA*, *LRRK2*, *GBA*, *PINK-1*, and *DJ-1* were excluded using previously described methods.^{6,7} Postmortem examination showed severe neuronal loss in the substantia nigra pars compacta and locus coeruleus (Fig. 1A). In the substantia nigra the density of Lewy body-containing neurons was decreased at least in part because of this severe neuronal loss. In contrast, in the amygdala, where there was relative preservation of neuronal density, there was a severe α -synuclein burden. The Braak stage for Lewy bodies was assigned 6/6 and

that of neuronal tangles was 1/6. There were no plaques consistent with pathological changes of Alzheimer's disease (CERAD score 0). While the above pathological features were typical of long-duration sporadic PD, additional findings were less typical: Lewy bodies involved all sectors of the hippocampus, putamen, and ambient gyrus; and some were large (diameter up to 72µm compared to the normal range of 2–40µm⁸) and irregularly shaped (Fig. 1C). Furthermore, consistent with previous autopsy studies of parkin disease,⁹ the degree of neuronal loss in the substantia nigra was severe.

Lewy bodies, though relatively rare in parkin disease, do occur. They were described in 5 of 18 carriers of two mutations, three of which had one p.R275W mutation.^{10–12} Their presence also seems to be associated with later onset of disease, as in our case.¹¹ The only other autopsy study of a heterozygous *PARKIN* carrier (p.R275W) also demonstrated diffuse Lewy bodies; and consistent with the above observation, symptom onset was at 62.⁵ Several explanations have been proposed for the inconsistent presence of Lewy bodies in parkin disease: a) the Lewy bodies that accumulate in these older patients are incidental as is seen with increasing age,¹¹ b) patients with late-onset disease lack the mechanisms to clear protein accumulation,¹³ and c) the mutations in these cases result in only partial loss of parkin ubiquitin E3 ligase function – the R275W mutation, for instance, has been postulated to be associated with residual ligase activity.¹¹ Less clear in this case is the association between dementia and the *PARKIN* exon 3-4 deletion since dementia is not typical of parkin disease.¹⁴ This is in contrast to sporadic PD where up to 75% of patients develop dementia 10 years after the diagnosis.¹⁵ In fact, carriers of 2 mutations with average disease duration of 26 years demonstrated better cognitive performance than non-carriers with early-onset PD.⁶ However, data in heterozygote carriers with long disease duration are lacking.

Overall, we think that the exon 3-4 deletion in our case was unlikely an incidental finding considering 1) that the mutation in the compound heterozygote cousins was associated with early-onset PD (and therefore, is likely pathogenic), 2) the relatively early onset of symptoms, slow progression and excellent response to relatively low doses of levodopa, which are features of parkin disease, and 3) the presence of clinical and pathological features not typical of sporadic PD. We cannot however rule out the possibility of co-existing sporadic Parkinson's and parkin disease.

Whether heterozygous *PARKIN* mutations are a risk factor for PD remains unknown, but in this family, a disease-associated heterozygous mutation was found in a patient with early-onset, slowly progressive Parkinson's disease with Lewy bodies and very late development of dementia. This case adds to the broadening pathological and clinical phenotype of *PARKIN*-associated PD.

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Figure 1. Pathological features

Hematoxylin-eosin staining shows severe neuronal loss in the substantia nigra (original magnification $\times 400$) (A); α -synuclein immunohistochemistry staining shows 3 Lewy bodies in the cingulate gyrus (original magnification $\times 200$) (B); α -synuclein immunohistochemistry staining shows a large irregular Lewy body in the substantia nigra (original magnification $\times 630$; scale bar $35\mu\text{m}$) (C).