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CORRESPONDENCE

Lewy body pathology and typical Parkinson disease in a patient with a heterozygous (R275W) mutation in the Parkin gene (*PARK2*)

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There are only two reports of neuropathological findings in heterozygotes for Parkin (*PARK2*) mutation [3, 5]. One was a normal individual bearing an exon 3 deletion, who at autopsy (at age 93) revealed the absence of α-synuclein pathology and no neuronal depletion in the substantia nigra (SN). The other case carried a single point mutation (C212Y, exon 6) and had been affected by neuropathologically confirmed PSP.

We here report a patient with a heterozygous Parkin mutation (R275W, on exon 7), clinical features of typical Parkinson's disease and a neuropathological picture of diffuse Lewy body disease. This patient had two offspring with compound heterozygous (R275W and exon 3 deletion) Parkin mutations (Fig. 1), both of which were affected by early-onset PD ([6], family 48). To our knowledge, this is the first report of diffuse Lewy body pathology associated with clinically typical PD in a patient with a heterozygous Parkin mutation.

A 62-year-old man presented with asymmetric fine motor impairment and rigidity, which were followed by resting tremor. There was good, sustained response to levodopa. Single photon emission computed tomography with Ioflupane (SPECT-DaTSCAN), performed 14 years from disease onset, showed severe reduction in tracer uptake in the corpora striata (Fig. 2a). Fifteen years after disease onset, the patient gradually became demented. This was confirmed by neuropsychological testing (MMSE 19/30; ADL 2; IADL 2), while neuroimaging at this time showed diffuse atrophy on brain MRI (Fig. 2b) and diffuse cortical and subcortical hypoperfusion on ECD-Tc99m-SPECT. He died at the age of 80.

At autopsy, macroscopic examination of the brain revealed bilateral depigmentation of the SN and locus

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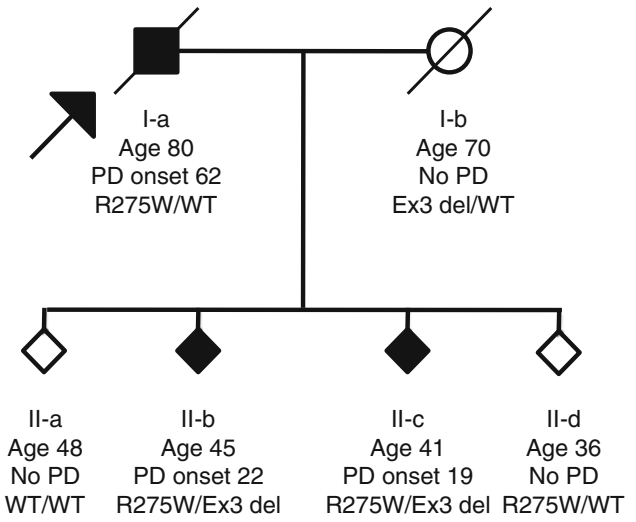

Fig. 1 Partial pedigree of Parkin heterozygote. Family members are disguised, except for proband (*arrow*) and spouse. Mutational status is reported for each member. Cases affected by PD are shown in *black*, with age at onset

coeruleus (LC). The following brain regions were sampled for microscopic investigation: medulla, pons, midbrain, hippocampal formation, amygdala, basal nucleus of Meynert, caudate nucleus, putamen and globus pallidus, thalamus, gyrus cinguli, temporal, insular, frontal, parietal, and occipital cortex, and cerebellum (including dentate nucleus). Routine staining with hematoxylin-eosin as well as immunohistochemistry with monoclonal antibodies to phosphorylated tau (AT8, 1:1000, Thermoscientific), α-synuclein (4D6, 1:2500, Signet, Dedham, MA, USA), and Aβ (4G8, 1:4000, Signet) were carried out. Gene sequencing and quantification analysis confirmed heterozygosity of the R275W mutation and excluded exon deletions or duplications.

Microscopically, there was severe neuronal depletion in the SN and LC (Fig. 2c), where numerous α-synuclein-immunoreactive Lewy bodies (LBs) and neurites were present (Fig. 2d). LBs and neurites were present in the dorsal nucleus of the vagus nerve and were also abundant in the reticular formation of the pons and medulla. LBs were numerous in the nucleus basalis of Meynert, while only a few alpha-synuclein positive neuronal inclusions were found in the striatum. At the cortical level, there was a high density of LBs and neurites in the uncal cortex (Fig. 2e), the subiculum and the temporal isocortex and, to a lesser degree, the cingulate, insular and frontal cortex. The topographical distribution of Lewy body pathology was compatible with Braak stage 6, according to BrainNet Europe Consortium guidelines [1]. There was an intense, widespread cortical deposition of Aβ, mostly as diffuse plaques, involving frontal and temporal (middle and

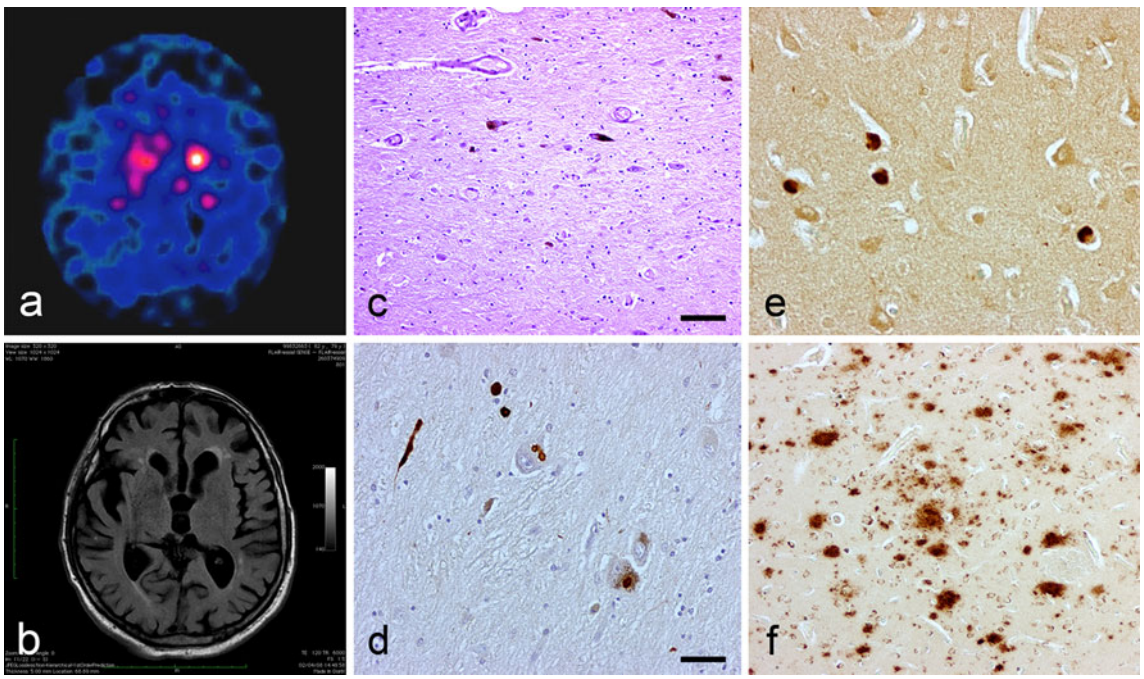

Fig. 2 Neuroimaging and neuropathology of Parkin (R275W) heterozygote. DaTSCAN showing marked reduction in tracer uptake in the corpora striata, more so in the putamina (**a**); brain MRI showing cortical and subcortical atrophy and ischemic changes in the periventricular white matter (**b**); Neuropathology (**c**–**f**): neuronal depletion in the substantia nigra (SN) (hematoxylin-eosin) (**c**); α-synuclein immunoreactive Lewy bodies and Lewy neurites in the SN (4D6) (**d**); high density of Lewy bodies in the uncal cortex (4D6) (**e**); diffuse Aβ plaques in the caudate nucleus (4G8) (**f**); *Scale bar* in **c**, 100 μm (c and f are the same magnification); *scale bar* in **d**, 50 μm (**d** and **e** are the same magnification)

superior gyri) regions; moderate deposition of small diffuse plaques was present in the striatum, with greater involvement of the caudate nucleus compared to the putamen (Fig. 2f). Tau immunohistochemistry disclosed intraneuronal deposits (pre-tangles) at the levels of the subiculum, transentorhinal and entorhinal cortex.

A recent comprehensive population genetic study on parkin mutations reported similar frequencies of heterozygous mutations between PD patient and control groups [4]. However, all the mutations found in the control group were in exons 1-4, while in the PD group, mutations were found in exons 2-9, where the coding regions for the highly conserved functional regions of *PARK2* are located, which suggests that the location of the single mutation may be important [4]. Interestingly, the two clinically manifest heterozygous Parkin mutations reported in the literature were located in exons 6 and 7 ([5] and our case, respectively). Furthermore, the R275W mutation has been shown to cause the formation of cytoplasmic and nuclear inclusions in cultured cells while retaining in vitro ubiquitinating activity [2]. The pathogenicity of mutations may thus be due to mechanisms different from lack of ubiquitination, and aggresome formation by this form of mutated parkin may represent a dominant effect with a possible role in Lewy body formation. This mechanism could also explain the presence of Lewy bodies in a previously reported compound heterozygous individual, who had the R275W (putatively dominant) mutation in association with an exon 3 deletion [3]. In our patient, the association of a single Parkin mutation, typical PD and Lewy body pathology may represent a chance occurrence. However, the evidence for aggresome formation due to the R275W mutation in vitro lends support to the hypothesis of an active role of this mutation in PD pathogenesis.

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