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CORRESPONDENCE

Atypical parkinsonism of progressive supranuclear palsy–parkinsonism (PSP-P) phenotype with rare variants in *FBXO7* and *VPS35* genes associated with Lewy body pathology

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A total of 23 gene loci have been identified in association with Parkinson's disease (PD), but the neuropathological background has been described in only a few of them. We had recently an opportunity to study the pathological finding in case of atypical parkinsonism associated with rare sequence variants in the *FBXO7* and *VPS35* genes; the neuropathology associated with variants in these genes has not yet been described [9]. All steps of the study were approved by the local ethics committee of the University Hospital Olomouc.

This case was a member of a family with positive history of parkinsonism; the family originated from an area of the Czech Republic with a proven increased prevalence of parkinsonism [2, 8]. As described in our previous paper, the patient was an 83-year-old man who had atypical parkinsonism with a phenotype of progressive supranuclear palsy—parkinsonism (PSP-P) with onset at the age of 66 [1] (see Video). The disease manifested initially with the signs typical for L-DOPA responsive idiopathic PD and gradually progressed. Ten years following the disease onset, the bulbar symptoms, apraxia of gait, tendency to sudden falls, supranuclear gaze palsy, blepharospasm with apraxia of lid opening and executive dysfunction developed; finally, the typical clinical pattern of PSP-P was present. There were no clinical features suggestive of diffuse Lewy bodies, such as REM sleep behavior disorder, visual or auditory hallucinations, or fluctuations of symptoms. When molecular genetic examination was performed, rare sequence variants of the vacuolar protein sorting 35(*VPS35*) gene (c.102 + 33G > A, rs192115886) and the F-box only protein 7(*FBXO7*) gene (c.540A > G, rs41311141) were identified in heterozygous state by massive parallel sequencing using Ion Torrent technology and confirmed by Sanger sequencing. The *VPS35* c.102 + 33G > A gene variant was also confirmed in the patient's cousin, who has late-onset Parkinson's disease with the usual phenotype [1]. Effect of this intron variant was tested using in silico predictive tools Human Splicing Finder and NetGene2. NetGene2 tool indicated possible breaking of acceptor splicing site. Enhancer/silencer predictors indicated possible breaking of splicing enhancer motif. Therefore, we could presume a probable variant effect on the splicing. Using the Human Splicing Finder and the predicted possible new splicing enhancer site, the variant *FBXO7*: c.540A > G located in the coding sequence was evaluated as likely benign according to ClinVar. Similar to the *VPS35* variant, the impact on RNA splicing can be expected. Pathogenicity of the identified variants remains to be proven, further functional studies are warranted as well.

After the patient died, a detailed neuropathological examination of the brain was conducted. At autopsy, the brain showed mild diffuse atrophy, the substantia nigra and locus coeruleus were depigmented (Fig. 1a). The 5 µm-thick sections of formalin-fixed paraffin-embedded tissue from specific regions of the brain were examined: frontal, temporal, parietal, occipital, and motor cortices, cingulate

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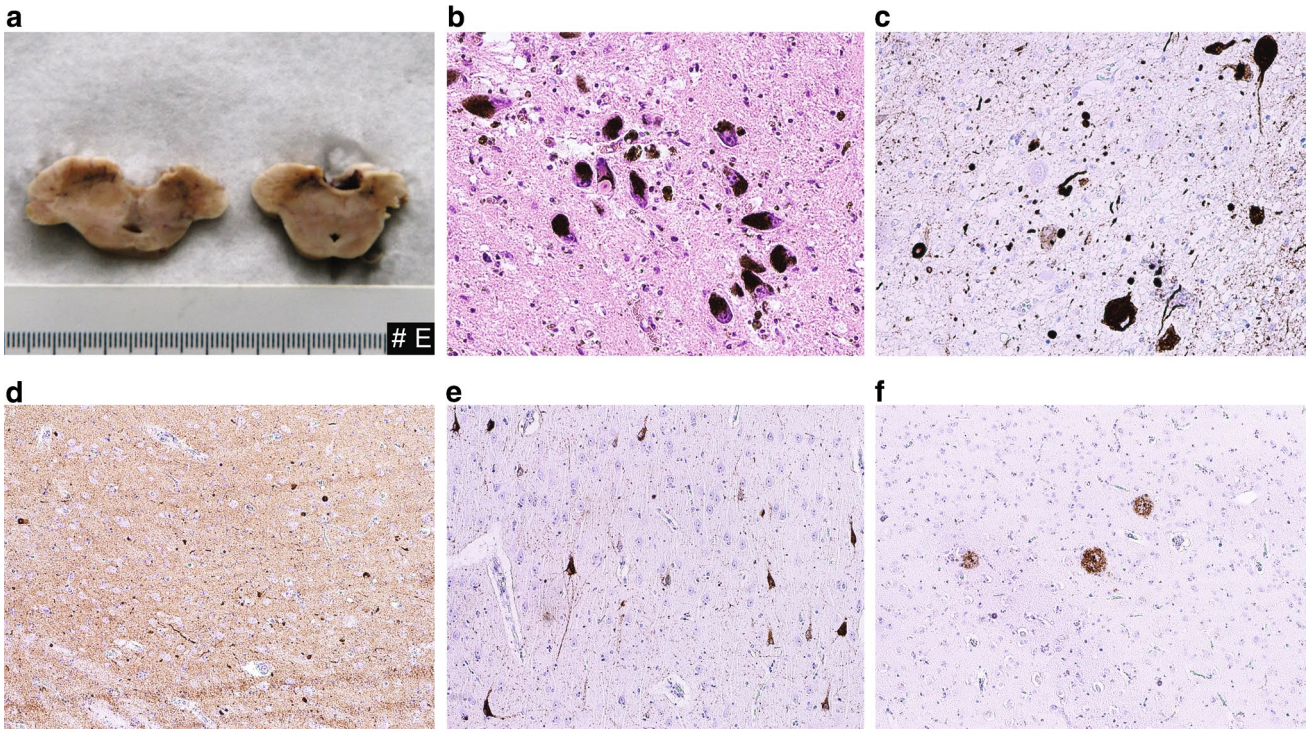

Fig. 1 **a** Depigmentation of substantia nigra. **b** Lewy body in the pigmented neuron of substantia nigra (H&E). **c** Spectrum of α-synuclein pathology in the pons: Lewy bodies, neuronal granular cytoplasmic positivity, thick and thin dystrophic neurites and dots (α-syn). **d** Numerous dystrophic neurites, dots, and neuronal granular cytoplasmic positivity in the amygdala (α-syn). **e** Spectrum of tau pathology in the hippocampus: pre-tangles and threads (AT8). **f** Sparse amyloid plaques in the occipitotemporal gyrus (β-amyloid)

gyrus, hippocampus and parahippocampal region, basal ganglia, thalamus, midbrain at the level of the substantia nigra, pons, medulla oblongata at the level of the inferior olivary nucleus, and cerebellum. In the routine hematoxylin and eosin staining, loss of neurons associated with gliosis and classic Lewy bodies were found in the substantia nigra (Fig. 1b). The immunohistochemical examination revealed α-synuclein positivity in the following regions: midbrain, pons, medulla, basal ganglia, amygdala, hippocampus and cingulate gyrus, and neocortical regions (frontal, temporal, and parietal cortices). In the brainstem, abundant Lewy bodies and pale bodies were identified, as well as granular cytoplasmic positivities, dots, and numerous thick or thin dystrophic Lewy neurites (Fig. 1c) Lewy body pathology was also present in the periaqueductal gray matter in the nucleus, which are involved in the supranuclear control of gaze. Many α-synuclein-positive pathological deposits were also found in the limbic regions, especially in the amygdala and in the cingulate gyrus but also in neocortical areas (Fig. 1d). The hippocampus was affected less consistently. In addition to predominant α-synuclein pathology, several tau-positive pathological inclusions (threads and pre-tangles) were found in the amygdala and hippocampus (Fig. 1e). There were also sparse beta-amyloid positive plaques in the occipitotemporal gyrus (Fig. 1f). In conclusion, the overall pathological picture corresponded to the diffuse neocortical type of Lewy-related pathology or Braak stage 6 of Parkinson`s disease with minor concomitant Alzheimer-type pathology (A1B1C0).

The *VPS35* gene is important as it encodes a subunit of a retromer involved in recycling cell proteins. The retromer consists of the SNX-BAR domain and cargo recognition trimer (VPS26, VPS29 and VPS35). The only confirmed pathogenic variant in the *VPS35* gene associated with PD is c.1858G > A (p.Asp620Asn), although a number of nearby variants are thought to potentially affect the same protein function [4, 5]. The rare *VPS35* variant (c.102 + 33G > A), identified in this family is located in the area of the transcribed protein that is thought to interact with a different part of the retromer complex (VPS26, VPS 29). Rare variants in VPS26 have already been associated with Parkinson's disease [6] and therefore, abnormalities in this part of the protein complex could be important for the development of the neurodegenerative process. The dysfunction of *FBXO7* protein results in defect of the ubiquitin proteasome system causing neuronal degeneration. In the past, several cases with variants in the *FBXO7* gene have been described; the clinical phenotype varied but was mostly dominated by early onset parkinsonism accompanied by pyramidal symptoms [3]. The variant (homozygous c.101 T`G) associated

with typical late-onset L-DOPA responsive parkinsonism, therefore, features differently when compared with recently described reports [7]. *FBXO7* is a distinctive gene with regard not only to clinical manifestation but also to the role it plays in numerous functions such as mitophagy, proteasome regulation, and mitochondrial maintenance related to SNCA, parkin, and PINK1 genes [3]. Further studies of these mutations may yield the potential to solve the molecular-pathological mechanisms of PD.

Unlike previously described phenotypes associated with variants in the *VPS35* and *FBXO7* genes [3, 10], the clinical picture in this case corresponded to PSP-P. This phenotype was probably the result of the significant impairment of brainstem structures including the periaqueductal gray matter and the structures involved in the control of vertical gaze, probably the interstitial nucleus of Cajal. In summary, this case provides the first description of a neuropathological correlation of parkinsonism associated with *VPS35* and *FBXO7* gene mutations and reveals Lewy body type α-synuclein pathology as a hallmark feature.

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Conflict of interest The authors declare that they have no conflict of interest.

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