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Valosin-containing-protein pathogenic variant p.R487H in Parkinson's disease

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ABSTRACT

We describe a 66-year-old woman with Parkinson's disease, carrying a known pathogenic missense variant in the Valosin-containing-protein (*VCP*) gene. She responded excellently to L-dopa, had no cognitive or motoneuronal dysfunction. Laboratory analyses and MRI were unremarkable. Genetic testing revealed a heterozygous variant in *VCP*(NM_007126.5), chr9 (GRCh3 7):g.35060820C > T, c.1460G > A p.Arg487His (p.R487H).

Parkinson's disease (PD) is a complex neurodegenerative disorder with ~ 10 % recognized as familial and an increasing number of identified causative, risk-associated genes. *Valosin-containing-protein* (*VCP*) gene encodes for VCP/p97, a ubiquitous ATPase from the AAA + family, which functions as a molecular "chaperone" assisting protein degradation via the ubiquitin–proteasome system, autophagy, membrane fusion, transcription activation, and apoptosis (Fig. 1). *VCP*-variants can induce misfolded protein inclusions that disrupt cellular mechanisms. VCP occurs in nuclear inclusions of Huntington's disease (HD), Lewy-body disease (LBD), Alzheimer's disease (AD), Creutzfeldt-Jacob disease (CJD) and amyotrophic lateral sclerosis (ALS) with dementia.

Over 80 *VCP* gene-variants are described in different central and peripheral neurological disorders [1]. Heterogenous clinical phenotypes of *VCP*-variants have been grouped into an entity called VCP-Multisystem-Proteinopathy (VCP-MSP) [2,3]. VCP-MSP is transmitted in an autosomal-dominant pattern, often caused by *VCP*-missense variants [2]. Physicians identify VCP-MSP when ≥ 2 of the following are present: inclusion-body-myopathy (IBM), Paget's bone disease (PBD), ALS, or frontotemporal-dementia (FTD).

A cohort of 231 patients from 36 *VCP* variant-harboring families showed 4 % of VCP-MSP patients with parkinsonism in their disease phenotype. Another large study investigated the role of *VCP* in 768 PD patients, found heterozygous *VCP*-variants in 1.4 % of the cohort, but no identified pathogenic variants. One case of idiopathic-like, levodopa-responsive PD was reported in a p.R159C-*VCP*-variant carrier [4]. This patient had a familial history of IBMPFD, and despite no muscle weakness, biopsy revealed changes consistent with IBM. The literature offers no other case of isolated parkinsonism.

Herein, we report a 67-year-old woman with typical levodopa-responsive idiopathic PD, harboring a p.Arg487His (p.R487H) *VCP*-variant. She was of Northern European descent; her parents, siblings, 5 adult children and 10 grandchildren were all healthy (except one with diabetes mellitus type 1). Motor symptoms started at age 62, when postural instability and gait difficulties on uneven ground appeared. She then developed loss of dexterity in the left upper-limb, left-limb rigidity, and emotional lability without mood changes. She suffered from severe constipation from age 65, sleep vocalization and screams, without dream enactment; however, polysomnography was not performed. The patient had a left-hand rest-tremor and left-arm rigidity. Her gait stride was shortened with decreased left-arm swing. Pull sign was positive. Her off-state MDS-UPDRS III was 7/56 and she was at Hoehn and Yahr Stage 1 at time of diagnosis. There were no orthostatic symptoms, anosmia, bulbar symptoms, cognitive complaint, no motoneuron nor muscular involvement. Her laboratory analyses, including complete blood count, basic blood chemistry, TSH, CPK, lipid panel, immunoglobulins, serum protein studies, were unremarkable. Brain MRI revealed no brain atrophy nor basal ganglia signal abnormality. A gene panel (94 genes related to PD included), revealed a heterozygous c.1460G > A (p.Arg487His) variant in the *VCP* gene, previously described as pathogenic in patients with VCP-MSP. This missense-variant was classified as "likely-pathogenic" according to ACMG guidelines. Started on carbidopa-levodopa (550 mg/day), the patient improved significantly without response fluctuations or side-effects.

VCP-variants account for 1–2 % of familial ALS [1]. In an ALS family with a p.R191Q-*VCP*-variant, one member (of unknown *VCP* status) presented with dementia, parkinsonism, PBD, and upper-limb muscle-weakness [1]. Another study described an ALS family with a p.R191G-*VCP*-variant, with 3 carriers presenting with ALS and parkinsonism. This study also reported a family with VCP-MSP and a p.R155H-*VCP*-variant, with one member (of unknown VCP status) having isolated parkinsonism.

VCP-variants appear in families with IBMPFD (now VCP-MSP) with extensive phenotypic heterogeneity. In a VCP-MSP family (p.R191Q-*VCP*-variant), a carrier presented with ALS, parkinsonism, and dementia, with Lewy bodies on autopsy. Another relative (of unknown *VCP* status) developed myopathy and then parkinsonism. In another VCP-MSP family with a p.T262A-*VCP*-variant, one carrier with FTD later developed parkinsonism, with Lewy-neurites upon autopsy. Another carrier member presented with early-onset parkinsonism from age 44 and lower-limb muscle weakness. *VCP*-variants have also been described in cases of CMT2 without parkinsonism.

We detected the *VCP*-p.R487H-missense variant in D2, an ATPAse functional domain, a variant appearing in sporadic and familial ALS. One carrier had ALS followed by FTD. His brother, of unknown *VCP* status, had FTD and parkinsonism. Another ALS-FTD patient carried *VCP*-variant p.R487H without parkinsonian features and with a family

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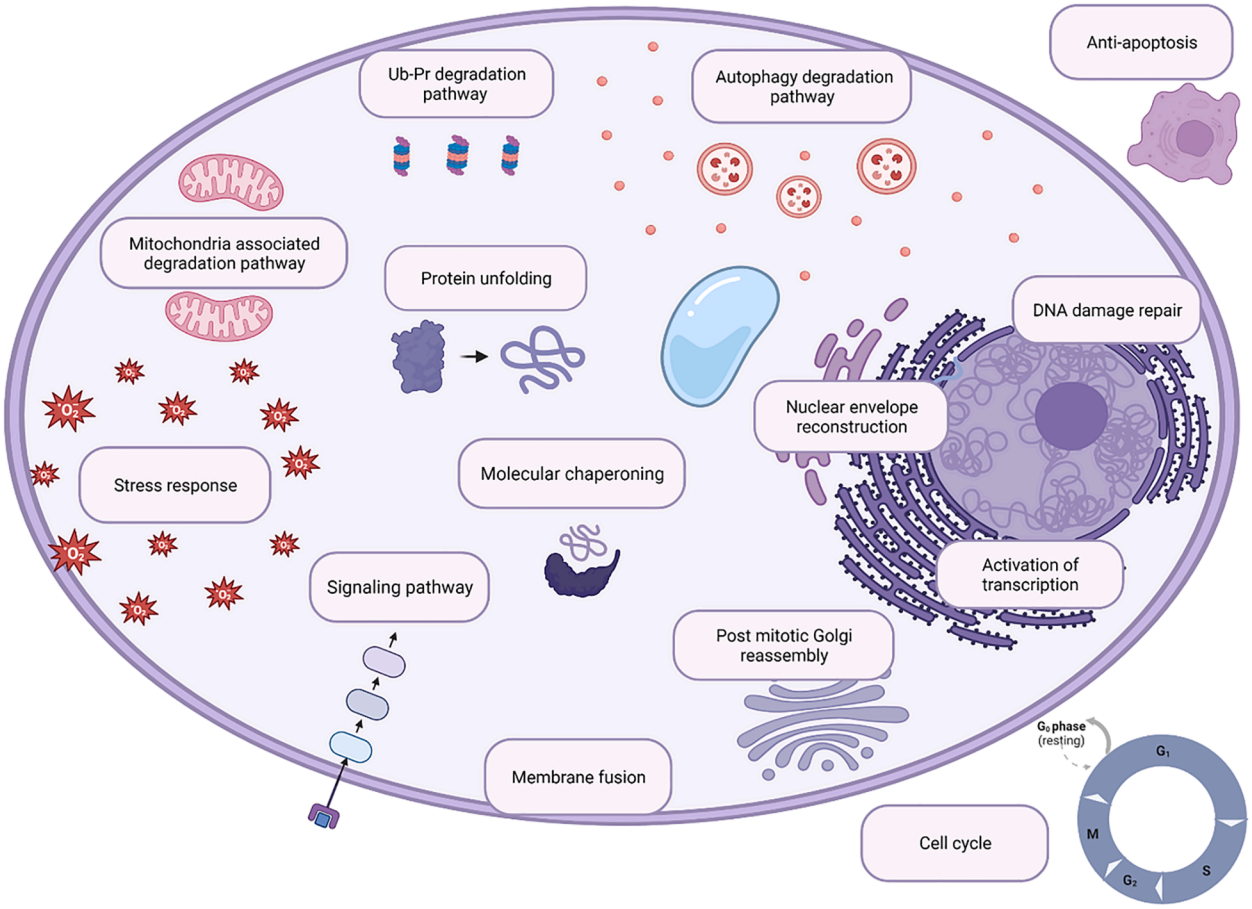

Fig. 1. VCP cellular functions. Ubiquitin-Proteasome degradation pathway. Autophagy degradation pathway. Mitochondria associated degradation pathway. Protein unfolding. Stress response. Molecular chaperoning. Signaling pathways. Membrane fusion. Post-mitotic Golgi reassembly. Nuclear envelope reconstruction. Activation of transcription. DNA damage repair. Apoptosis. Cell cycle.

history of ALS; autopsy revealed no alpha-synucleinopathy. These two cases highlight the pathogenicity of the p.R487H *VCP*-variant, despite clinical and pathological phenotype heterogeneity. The overall frequency of this variant is 0.001 %, including 4 heterozygotes, with a frequency of 0.002 % in Non-Finnish European sub-populations. An in silico *meta*-predictor suggests that this amino acid change may impact protein function. This result is supportive of a diagnosis of a VCP-related disorder for our patient. We cannot exclude the presence of other genetic (e.g. an additional variant) or non-genetic factors influencing the penetrance of this p.R487H-variant and our patient's phenotype. Also, normal electrophysiological findings and imaging can help support the diagnosis of dopa-responsive PD. Furthermore, in cases with atypical parkinsonism, additional tests such as a brain MRI and DAT-scan are absolutely recommended to confirm the clinical phenotype.

Studies reported that the arginine of codon 487 is highly conserved across species. *VCP*-variants increase neuronal sensitivity to oxidative stress, which may explain the cellular dysfunction leading to PD in our case. However, thorough functional testing of R487H and comparison to other VCP-mutations are needed to confirm pathogenicity. While the exact mechanisms of VCP-mutations are debated, several recent studies suggest an underlying loss of VCP function. In this context, a decrease in *VCP* expression might presage preclinical and early clinical PD stages [5].

Given *VCP* presence in nuclear inclusions with HD, LBD, AD, CJD, and ALS with dementia, we hypothesize that our case also shows *VCP*-inclusions in the substantia nigra, leading to a levodopa-responsive parkinsonian phenotype (to be determined upon autopsy). Despite our case showing no evidence of frontal syndrome or motor dysfunction, follow-up will determine future development of further symptoms of the MSP-spectrum.

In conclusion, we report a case of idiopathic-like Parkinson's with a *VCP*-p.R487H-variant, highlighting *VCP*'s potential role in the PD pathogenic pathway even in sporadic cases of the disease presenting solely with dopa-responsive "typical" parkinsonism. In this case, we cannot exclude the possibility offuture development of further symptoms.

Permissions: The patient gave written, informed consent for the use of her deidentified data for research purposes.

Disclosures:

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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