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Mutational analysis of the *VCP* gene in Parkinson's Disease

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Abstract

Mutations in the valosin-containing protein gene (*VCP*) have been identified in neurological disorders (IBMPFD and ALS) and are thought to play a role in the clearance of abnormally folded proteins. Parkinsonism has been noted in kindreds with *VCP* mutations. Based on this, we hypothesized that mutations in *VCP* may also contribute to idiopathic PD. We screened the coding region of the *VCP* gene in a large cohort of 768 late onset PD cases (average age at onset = 70 years), both sporadic and with positive family history. We identified a number of rare single nucleotide changes, including a variant previously described to be pathogenic, but no clear disease-causing variants. We conclude that mutations in *VCP* are not a common cause for idiopathic PD.

1. Introduction

A member of the AAA+ ATPase family, *VCP* is a highly conserved, ubiquitously expressed protein that is known to be involved in a wide variety of key cellular processes. In proteinopathies, *VCP* is thought to play a central role in the ubiquitin-proteasome and autophagy degradation pathways (Ju and Weihl, 2010). A number of observations support the involvement of *VCP* in the pathogenesis of neurodegeneration and suggest a dominant-negative effect for *VCP* mutations that lead to mislocalization and impaired removal of

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Disclosure Statement

None

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TDP-43 protein (Shaw, 2010). First, mutations in the valosin-containing protein gene (*VCP*) cause a multisystem degenerative disorder affecting muscle, brain and bone tissues known as inclusion body myopathy - early Paget's disease of the bone - frontotemporal dementia (IBMPFD; Watts et al., 2004). TDP-43 pathology has been observed in IBMPFD cases (Weihl et al., 2008; Neumann et al., 2007) and *VCP*-mutant mouse models of the condition (Ju et al., 2009; Custer et al., 2010). Pathological TDP-43 inclusions are also found in Perry syndrome, a rare autosomal dominant disorder with features of Parkinsonism (Wider et al., 2009). Second, we recently extended the phenotype spectrum of *VCP* mutations to include motor neuron degeneration in the form of familial ALS with TDP-43-positive inclusions (Johnson et al., 2011). The observation of concomitant Parkinsonism symptoms in some members of IBMPFD families (Johnson et al., 2011) led us to hypothesize that mutations in *VCP* may also contribute to idiopathic PD. To test this, we performed mutational screening of *VCP* in a large cohort of PD cases.

2. Methods

The PD and control cohorts were sequenced for all 17 exons of the *VCP* gene, as previously described (Full methods presented in supplementary data).

3. Results

A total of 768 late-onset PD subjects, including 244 cases with a positive family history, were screened for *VCP* mutations. All variants found in the cohort are listed in Supplementary Table 1. These substitutions were either silent or in a non-coding region of the gene and are less likely to affect the protein. However, the variants are novel and their frequency in control populations is unknown. We identified a (c.468A>G, p.I27V) variant in one case, which had been previously reported to be potentially pathogenic (Ju and Weihl, 2010; Rohrer et al., 2011). In-house 3D model analysis of p.I27V showed that amino acid I27 lies close to the cluster of known pathogenic mutation and that, a change to valine may affect interaction with neighbouring monomers, in the *VCP* hexamer configuration. However, this p.I27V variant was also present in two neurologically normal individuals (out of 716 sequenced controls, Coriell sample IDs: ND02653 and ND02773) raising questions about its pathogenicity. These "neurologically normal" individuals were aged 41 and 82 years of age at the time they were classified and DNA was collected, but their current medical status at present with respect to Paget's disease of bone, inclusion body myopathy, or neurological disease is unknown. Although these variants were novel and rare, they are unlikely to be responsible for disease in these individuals.

4. Discussion

We report the first comprehensive mutation screening of the *VCP* gene in a large cohort of PD patients. Heterozygous variants were present in ~1.4% of PD cases, but no clearly pathogenic mutations were identified. The majority of these had not been reported in the dbSNP or 1000 Genomes online databases of variants (<http://www.ncbi.nlm.nih.gov/projects/SNP/>; <http://www.1000genomes.org/>). It is possible that our cohort was underpowered to identify rare mutations in this gene. PD with TDP-43 CNS pathology account for less than 10% of cases (Nakashima-Yasuda et al., 2007) and such cases may represent a more suitable subset of patients for screening for *VCP* mutations. However, overall our data show that genetic variants in *VCP* are not commonly associated with PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

See Supplementary Material

References

See Supplementary Material