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NOVEL p.Ile151Val MUTATION IN VCP IN A PATIENT OF AFRICAN AMERICAN DESCENT WITH SPORADIC ALS

The valosin containing protein (VCP) is a member of the AAA-ATPase family, a group of enzymatic molecular chaperones that have been associated with a range of cellular processes including ubiquitin-proteasome mediated degradation, membrane fusion, apoptosis, cell-cycle control, and autophagy.¹ Mutations in *VCP* were first identified to cause familial inclusion body myopathy with early-onset Paget disease and frontotemporal dementia² (IBMPFD) and more recently were found to be implicated in familial amyotrophic lateral sclerosis (ALS).³ It was suggested that *VCP* mutations may account for 1%–2% of familial ALS cases.³ Whether *VCP* mutations also contribute to sporadic ALS (SALS), however, has not yet been studied. Here, we report the identification of a novel p.Ile151Val mutation in *VCP* in a patient of African American descent with SALS.

Case report. In the course of screening patients with ALS ascertained by the ALS Center at Mayo Clinic Florida (MCF) for mutations in the known ALS genes (*SOD1*, *TARDBP*, *FUS*, *OPTN*, and *VCP*), we identified an African American patient with the c.451A>G mutation in exon 5 of *VCP* predicted to result in the p.Ile151Val substitution. Mutations were excluded in all other exons and genes analyzed in this patient. The *VCP* p.Ile151Val mutation was not previously reported in dbSNP or the 1000 Genomes databases and genotyping using a custom-designed ABI Taqman assay excluded this mutation from 407 healthy African American controls obtained from MCF (n = 317) and the Coriell Institute for Medical Research (n = 90). Mutations in *VCP* exon 5 in an additional 112 patients with ALS (including 96 SALS) were excluded.

The patient developed progressive left lower limb weakness at the age of 68 years. Lower limb atrophy, lower limb spasticity, and diffuse hyperreflexia including hyperactive jaw jerk was evident on evaluation 4 months after onset of motor symptoms. She had a medical history of hypertension and increased serum cholesterol but had otherwise been healthy.

EMG examination at that time showed fibrillation and fasciculation potentials and signs of chronic partial motor denervation and reinnervation in cervical, thoracic, and lumbosacral segments. MRI of the brain and spine showed no contributory lesions. There was no focal atrophy on brain MRI. On initial evaluation diagnostic criteria were met for El Escorial clinically probable ALS. Upper and lower motor neuron signs progressed, including progression of spasticity in bulbar and upper limb muscle groups, leading to loss of functional speech, gastrostomy tube placement at 17 months, and respiratory compromise treated with initiation of bilevel noninvasive ventilation at 19 months after onset of motor symptoms. Amyotrophic Lateral Sclerosis Functional Rating Scale–revised score of 38 declined by approximately 1.2 points per month, and forced vital capacity of 107% predicted declined by over 6% per month during follow-up from initial evaluation 7 months after disease onset through death 23 months later.⁴ She did not develop pseudobulbar affect or apparent cognitive impairment, although the latter was not formally assessed. Tracheostomy was not performed. The patient died at age 70 years, 30 months after onset of motor symptoms. Postmortem examination was not performed.

The patient's mother was living independently at age greater than 90 years at the time of the patient's death; the father died of colon cancer at age 76. There was no family history of ALS, dementia, muscle disease suggestive of inclusion body myositis, or bone disorders including Paget disease.

Discussion. We report the identification of a novel *VCP* p.Ile151Val mutation in an African American patient with SALS. Limited data are available on the prevalence and distribution of *VCP* mutations in ALS, with only a single study reported to date.³ We are aware of no other reports of *VCP* mutations associated with ALS in African Americans, nor in patients with ALS without a known family history of the disease. Our patient met diagnostic criteria for classic ALS with survival of 30 months from onset of weakness. The *VCP* p.Ile151 amino acid residue is highly conserved across species (figure). Despite the conservative amino acid substitution, the

Figure Novel VCP p.Ile151Val mutation identified in this study

Chromatograms of the mutant and a wild-type sequence of VCP exon 5 are shown at the top. The corresponding VCP amino acid numbering is shown below the nucleotides. At the bottom, the evolutionary conservation of VCP is shown across species. The mutant amino acid residue 151 is highlighted with a red box.

p.Ile151Val mutation is located in the N-terminal cofactor-binding (N)-domain only 4 amino acid residues away from the most frequently mutated Arg155. This location is in agreement with recent studies suggesting that all mutant VCP residues cluster within the cleft that separates the N-domain from the adjacent AAA ATPase domain and may interfere with the movement of these domains throughout the ATPase cycle.⁵ We believe that this mutation contributed to the development of ALS in our patient, but recognize that pathogenicity cannot be proven by genetic studies alone. Additional research studies in DNA repositories of patients with SALS should be considered to determine the presence of p.Ile151Val or other VCP mutation carriers.

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