

Valosin-Containing Protein-Related Disorders via VCP Gene Sequencing (Test #597) Inclusion Body Myopathy with Early Onset Paget Disease and Frontotemporal Dementia Amyotrophic Lateral Sclerosis 14

Brief Description of Clinical Features: Inclusion body myopathy with early onset Paget disease and frontotemporal dementia (IBMPFD, OMIM 167320) is characterized by adult-onset proximal and distal muscle weakness, early onset Paget disease of bone, and frontotemporal dementia (Kimonis et al. *GeneReviews* 2011). Muscle weakness resembles that seen in limb-girdle muscular dystrophy, and respiratory and cardiac involvement may occur later in the disease course. Serum CK is typically normal or mildly elevated and EMG studies demonstrate myopathic changes (Kimonis et al. *Genet Med* 2:232-241, 2000). Symptoms of bone disease include pain of the spine and hip and enlargement and deformity of the long bones. Bone symptoms originate from focal abnormalities of increased bone turnover (Kimonis et al. *Am J Med Genet* 146A:745-757, 2008). Serum alkaline phosphatase levels are elevated as are urine pyridinoline and deoxypyridinoline concentrations. Early signs of frontotemporal dementia include social unawareness and disinhibition, expressive or receptive language dysfunction, and relative sparing of memory (Kimonis et al. *GeneReviews* 2011). IBMPFD is a progressive disease leading to disabling muscle and bone disease and inability to speak. An exome sequencing strategy revealed that familial amyotrophic lateral sclerosis with or without frontotemporal dementia (ALS14, OMIM 613954) results from mutations in the VCP gene (Johnson et al. *Neuron* 68:857-864, 2010).

Genetics: Inclusion body myopathy with early onset Paget disease and frontotemporal dementia is an autosomal dominant disorder with incomplete penetrance of the three clinical features (limb-girdle muscle weakness, Paget disease of bone, and frontotemporal dementia). Missense mutation of the VCP gene (OMIM 601023) are the only known cause of IBMPFD, and substitution of the Arg155 residue was shown to be the predominant mutation among North American patients (Watts et al. *Nat Genet* 36:377-381, 2004). ALS14 is also an autosomal dominant disorder.

Description of This Particular Test: Valosin-containing protein is coded by exons 1-17 of the VCP gene on chromosome 9p13.3. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. As indicated, we will also sequence any single exon (Test #100, \$190) in family members of patients with known mutations or to confirm research results. Exon 5 (encoding Arg155) may be sequenced before the remainder of the gene.

Reference Sequences:

	Genomic: NC_000009.11	mRNA: NM_007126.3
	Protein: NP_009057.1	mRNA and Protein: CCDS 6573.1

Indication for Testing: Patients with late onset and progressive proximal and distal muscle weakness, Paget disease of bone, and premature frontotemporal dementia.

Sensitivity of test: Sensitivity should be high in patients meeting clinical criteria for all three symptoms of IBMPFD. In one study, 10 of 13 affected families had a mutation involving Arg155 (Watts et al. *Nat Genet* 36:377-381, 2004). VCP mutations are probably a rare cause of ALS. Screening of the VCP gene in 210 familial ALS cases and 78 autopsy-proven ALS cases identified 3 mutations in 4 patients (Johnson et al. *Neuron* 68:857-864, 2010).

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of VCP Gene Exons 1-17 \$ 1060

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x 20	83898	\$ 320	Sequencing x 20	83904	\$ 485
Separation	83894	\$ 70	Interpretation/Report	83912	\$ 115

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

Contact for info: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com, www.preventiongenetics.com