Inclusion Body Myopathy with Paget Disease and/or Frontotemporal Dementia *VCP* sequence analysis

Disorder: Mutations in valosin containing protein (*VCP*) are responsible for inclusion body myopathy with Paget disease of bone and/or frontotemporal dementia (IBMPFD), a dominantly inherited disorder. Approximately 80% of affected patients have a family history of IBMPFD; however, there is significant variability, even within families. *VCP* is a member of the type II AAA-ATPase family and is involved in protein degradation, which, when mutated, leads to defective autophagy and ubiquitin-mediated protein degradation. Mutations in *VCP* cause dysfunction of mitochondria.

A diagnosis of IBMPFD should be considered when a patient has symptoms in two of three categories:

1. **Myopathy**
   - Myopathy has been reported in over 80% of individuals with a typical onset between 30-40 years
   - Begins with the muscles of the shoulder and hips and eventually progresses to quadriparesis with respiratory and cardiac failure
2. **Paget disease of the bone**
   - Identified in approximately 50% of individuals with IBMPFD, with a mean age of onset of 41.7 years
   - Often asymptomatic, but may present as pain, skeletal deformity or localized enlargement
3. **Frontotemporal dementia**
   - Approximately 30% of individuals with IBMPFD experience frontotemporal dementia with a mean age of diagnosis of 55.1 years
4. **Mutations in VCP have also been associated with familial amyotrophic lateral sclerosis (ALS) and familial frontotemporal lobar degeneration with ubiquitin-positive, tau-negative inclusions (FTLD)**

Indications:

- Patient with physical manifestation of IBMPFD
- Patient with familial ALS
- Patient with FTLD with characteristic inclusion findings
- Presymptomatic diagnosis and/or carrier testing in a relative of a patient with proven *VCP* mutation
- Prenatal diagnosis of an at-risk fetus (by prior arrangement only)

Additional information and test requisitions are available at: www.cchmc.org/molecular-genetics

Shipping Instructions:

Please enclose **test requisition** with sample.
All information must be completed before sample can be processed.

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday

Ship to:

Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

Cincinnati Children's
Human Genetics

Molecular Genetics Laboratory
CLIA#: 36D0656333
Phone: (513) 636-4474
Fax: (513) 636-4373
Email: moleculargenetics@cchmc.org
www.cincinnatichildrens.org/molecular-genetics

Specimen:

Blood: 3mL whole blood in purple top (EDTA) tube.

Cytobrush (buccal sample): 6 cytobrushes sent at ambient temperature. Please call for free cytobrush collection kit.

Label each item with patient's name, birth date, and date of collection.

Testing Methodology: PCR-based sequencing of the coding and exon/intron boundaries of the *VCP* gene.

Test Sensitivity:

Clinical Sensitivity: *VCP* is the only gene associated with IBMPFD. Approximately 2% of familial ALS is associated with *VCP* mutations. Missense mutations account for all reported mutations; large deletions, insertions and rearrangements have not been reported.

Analytical Sensitivity: The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Mutations in regulatory regions or other untranslated regions are not detected by this test. Large deletions involving entire single exons or multiple exons, large insertions and other complex genetic events will not be identified using this test methodology. Rare primer site variants may lead to erroneous results.

Turn-Around Time: 28 days

CPT Codes:

VCP full gene sequencing: 81479

Family specific mutation analysis: 81479

Please call 1-866-450-4198 for pricing, insurance preauthorization, or with any billing questions.

Results: Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

References:

Cairns, N. J. et al. (2007) Am J Pathol, 171(1), 227-40.

Hirabayashi, M. et al (2001) Cell Death Differ, 8(10), 977-84.

Ju, J. S. and Weihl, C. C. (2010) Hum Mol Genet, 19(R1), R38-45.

Kimonis, V. E. et al (2008) Biochim Biophys Acta, 1782(12), 744-8.

Nalbandian, A. et al (2011) J Mol Neurosci, 45(3), 522-31.

Watts, G. D. et al (2004) Nat Genet, 36(4), 377-81.