

Inclusion Body Myopathy-2, Autosomal Recessive and Nonaka Myopathy via *GNE* Gene Sequencing (Test #367)

Brief Description of Clinical Features: Inclusion Body Myopathy (IBM) is a heterogeneous group of disorders characterized by muscle fibers with rimmed vacuoles and inclusions consisting of filaments with a diameter of 15 to 21 nm (Griggs et al. *Ann Neurol* 38:705-713, 1995). Mutations in the *GNE* gene cause recessively inherited IBM (IBM2; OMIM #600737), the most common form of this disorder. IBM2 generally presents as a slowly progressive distal weakness in young adults in their second and third decades of life. Clinical presentation includes gait disturbance and foot drop secondary to anterior tibialis muscle weakness. Weakness eventually includes the hand and thigh muscles, but commonly spares the quadriceps muscles, even in advanced disease. Affected individuals are usually wheelchair bound approximately 20 years after onset (Sinnreich and Karpati, *GeneReviews*, 2006). Nonaka Myopathy (OMIM #605820), also called Distal Myopathy with Rimmed Vacuoles, is allelic to IBM2 and has a similar clinical phenotype, although more rapid progression has been reported (Nonaka et al. *J Neurol Sci* 51:141-155, 1981).

Genetics: Inclusion Body Myopathy (IBM2) and Nonaka Myopathy are allelic, autosomal recessive disorders caused by *GNE* mutations. A similar disorder caused by *MYH2* gene mutations and with autosomal dominant inheritance has also been reported (IBM3; OMIM #605637). Most *GNE* mutations are missense mutations affecting either the epimerase or kinase domain of this bi-functional enzyme; however, nonsense mutations, splice site mutations, and deletions are also known. IBM2 is the most common genetic disorder among Iranian Jews; the carrier rate may be as high as 1:15. Another allelic disorder, Sialuria (OMIM #269921), is an autosomal dominant inborn error of metabolism characterized by overproduction of cytosolic sialic acid. *GNE* mutations associated with this disease are restricted to codons 263-266 and are believed to cause inactivation of the negative inhibitory domain of UDP-N-acetylglucosamine 2-epimerase leading to toxic overproduction of N-acetylneuraminic acid.

Description of This Particular Test: The bi-functional enzyme UDP-N-acetylglucosamine 2-epimerase is coded by exons 1-12 of the *GNE* gene on chromosome 9p12. 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. Single exons known to harbor founder mutations can be sequenced for diagnostic and carrier testing.

Reference Sequences: Genomic: NC_000009.10 mRNA: NM_001128227.1 Protein: NP_001121699

Indication for Testing: Patients with clinical features consistent with Inclusion Body Myopathy, demonstrated autosomal recessive inheritance, and a muscle biopsy with characteristic immunohistochemical features.

Sensitivity of test: The exon 12 p.Met712Thr mutation is the only *GNE* mutation identified to date Among Middle Eastern Jewish individuals (Eisenberg et al. *Hum Mut* 21:99, 2003). In Japanese patients, the p.Val572Leu mutation in exon 10 is the most common mutation although others are known (Arai et al. *Ann Neurol* 52:516-519, 2002; Tomimitsu et al. *Neurol* 62:1607-1610, 2004).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *GNE* Gene Exons 1-12 \$ 780

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 13	83898 \$ 230	Sequencing x13	83904 \$ 330
Separation x1	83894 \$ 60	Interpretation/Report x1	83912 \$ 90

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

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