PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Mucolipidosis II and Mucolipidosis III Alpha/Beta via *GNPTAB* Gene Sequencing (Test #316)

Brief Description of Disorder: Mucolipidosis II (ML II) (OMIM 252500), also called Inclusion-cell or I-cell disease, is part of the lysosomal storage disease family. The disease manifest at birth, and patients typically do not survive past the first 1-2 years. Phenotypic characteristics include thickening of the skin, course facial features, hypertrophic gingival, thoracic deformities, clubfoot, kyphosis, hip dislocations, dysostosis multiplex and cardiac involvements. Death usually occurs due to respiratory insufficiency from stiffening of the thoracic cage (Leroy et al. GeneReviews, 2009, www.genetests.org). ML II can be differentiated from Mucolipidosis III alpha/beta (ML III α/β) (OMIM 252600) by earlier clinical onset and more severe phenotypic characteristics. ML III α/β, also called Pseudo-Hurler Polydystrophy, manifests clinically at approximately 3 years of age. Phenotypic characteristics include slow growth rate, moderate dysostosis multiplex, joint stiffness, mild coarsening of facial features, mild cognitive impairment. Cardiorespiratory complications are the common cause of death (Leroy et al. GeneReviews, 2009, www.genetests.org).

Genetics: ML II and ML III α/β are inherited in an autosomal recessive manner and are caused by mutations in *GNPTAB*, which encodes the enzyme alpha/beta GlcNAc-1-phosphotransferase. ML II mutations mostly result in premature translational termination (or nonsense mediated decay) (Tiede et al. Nat Med 11:1109-1112, 2005; Tappino et al. Mol Genet Metab 93:129-133, 2008). Nonsense, frameshift and splicing mutations are also common in ML III α/β, but missense mutations are more common than in ML II and are mostly localized to the protein recognition domain, leaving the catalytic domain with some residual activity (Bargal et al. Mol Genet Metab 88:359-363, 2006). Mutations in *GNPTAB* have also been associated with stuttering (Kang et al. N Engl J Med 362:677-685, 2010).

Description of This Particular Test: Testing is performed by determining and analyzing the deoxyribonucleic acid (DNA) sequence of the entire *GNPTAB* gene. This is accomplished by amplifying the 21 coding exons and ~50 of adjacent noncoding sequences using PCR followed by DNA sequencing using the dideoxy chain-terminating method of Sanger et al. in conjunction with a capillary electrophoresis apparatus.

Reference Sequences:	**Genomic: NC_000012.11**	**mRNA: NM_024312.3**
	Protein: NP_077288.2	**mRNA and Protein: CCDS 9088.1**

Indications for Test: For ML II, patients are candidates for this test if they have phenotypic symptoms common to ML II and show increased hydrolase (β-D-hexosamindase, β-D-glucuronidase, β-D-galactosidase, and α-L-fucosidase) activity and excessive excretion of oligosaccharides (Oss) in the urine. For ML III α/β, patients are candidates for this test if they have pheynotypic symptoms common to ML III α/β and show a significant decrease (90-99%) in UDP-N-acetylglucosamine enzyme activity as well as an increase in hydrolase (β-D-hexosamindase, β-D-glucuronidase, β-D-galactosidase, and α-D-mannosidase) activity. Excessive excretion of oligosaccharides (Oss) in the urine may occur but is not always present.

Sensitivity of Test: The sensitivity for the *GNPTAB* sequencing test is >95% for both ML II and ML III α/β.

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

SPECIMEN REQUIREMENTS: See page 4 of the Test Requisition Form.

Price: **Sequencing of *GNPTAB* Gene** **$ 1,240**

CPT Codes:

Sample Ascertainment x1	83890	$ 30	DNA Isolation x1	83891	$ 40
Amplification x24	83898	$ 380	Sequencing x24	83904	$ 580
Separation x1	83894	$ 90	Interpretation/Report x1	83912	$ 120

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

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