

Sialuria via *GNE* Gene, Exon 5 Sequencing (Test #368)

Brief Description of Clinical Features: Sialuria (OMIM #269921) is an autosomal dominant inborn error of metabolism characterized by accumulation and excretion of free sialic acid and normal or increased levels of neuraminidase activity (Seppala et al. *J Biol Chem* 266:7456-7461, 1991). The mechanism for excessive sialic acid synthesis is failure of feed-back inhibition of UDP-N-acetylglucosamine 2-epimerase by the pathway's end product N-acetylneuraminic acid (Thomas et al. *Pediatr Res* 19:451-455, 1985). Among a small number of reported patients, clinical features presented in the first few months of life and included hepatosplenomegaly, mildly coarse facies, mild motor delay, and massive urinary excretion of free N-acetylneuraminic acid (Seppala et al. *Am J Hum Genet* 45: A11, 1989; Leroy et al. *Am J Hum Genet* 68:1419-1427, 2001). The patients in this report had near normal growth and development, unlike patients with lysosomal storage of N-acetylneuraminic acid. This preservation of growth and development in Sialuria patients is thought to occur because the accumulated N-acetylneuraminic acid is mostly restricted to the cytosolic fraction (Seppala et al., 1989).

Genetics: 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. Allelic disorders are Inclusion Body Myopathy (IBM2) and Nonaka Myopathy. Both are autosomal recessive disorders.

Description of This Particular Test: The bi-functional enzyme UDP-N-acetylglucosamine 2-epimerase is coded by exons 1-13 of the *GNE* gene on chromosome 9p12. Testing for Sialuria is accomplished by amplifying exon 5 containing codons 263-266, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

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

Indication for Testing: Patients with clinical features consistent with Sialuria, urinary excretion of N-acetylneuraminic acid, and demonstrated autosomal dominant inheritance.

Sensitivity of test: Because of the relatively mild facial coarseness and preserved growth and development of this disorder, Sialuria is probably underdiagnosed (Leroy et al. 2001). More extensive urinary screening for free N-acetylneuraminic acid may be indicated in individuals, both children and adults, with mild developmental delay. All Sialuria patients thus far reported have had mutations in codons 263-266 in exon 5 of the *GNE* gene, which predicts the location of an allosteric regulatory site (Seppala et al. *Am J Hum Genet* 64:1563-1569, 1999).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of <i>GNE</i>	Exon 5	\$ 190
CPT Codes:			
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x1	83898 \$ 25	Sequencing x1	83904 \$ 35
Separation x1	83894 \$ 15	Interpretation/Report x1	83912 \$ 45

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

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