NGLY1 Deficiency: NGLY1 Gene Sequencing

Test Code: SGLY1  
Turnaround time: 6 weeks  
CPT Codes: 81479 x1

Condition Description

NGLY1 deficiency is a novel autosomal recessive disorder of the endoplasmic reticulum–associated degradation pathway associated with neurological dysfunction, abnormal tear production, and liver disease. The enzyme N-glycanase 1 (NGLY1), also known as peptide: N-glycanase (PNGase, EC 3.5.1.52), catalyzes protein deglycosylation by cleaving the \(\gamma\)-aspartyl glycosylamine bond of N-linked glycoproteins with the subsequent release of intact N-glycan species. Evidence suggests that NGLY1 participates as a key cytoplasmic component of the endoplasmic reticulum–associated degradation (ERAD) machinery along with the AAA ATPase complex p97. The ERAD pathway is a mechanism for identifying and degrading misfolded glycoproteins. N-glycans that are high in mannose content act as quality control tags for proteins in the early stages of the secretory pathway. Misfolded glycoproteins are detected by ER luminal lectins and are then translocated to the cytosol via the ERAD machinery to be subsequently degraded by cytosolic enzymes, including NGLY1. The majority of patients detected to date carry a specific nonsense mutation that appears to be associated with severe disease. The phenotypic spectrum is likely to enlarge as cases with a broader range of mutations are detected. NGLY1 deficiency is caused by mutations in the NGLY1 gene.

Reference:


Genes

NGLY1

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of NGLY1 deficiency.

Methodology

For Sanger sequencing:

PCR amplification of 10 exons contained in the NGLY1 gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

Detection

Full Gene Sequencing

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%.

Specimen Requirements

Type: Whole Blood

Specimen Requirements:

- In EDTA (purple top) tube:  
  - Infants (2 years): 3-5 ml  
  - Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Ship sample at room temperature with overnight delivery.

Type: Isolated DNA

Specimen Requirements:
In microtainer: 60 ug

Isolation using the Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping: Refrigerate until time of shipment in 100 ng/ul of TE buffer. Ship sample at room temperature with overnight delivery.

**Related Tests**

- Congenital Disorders of Glycosylation Gene Sequencing and Deletion/Duplication Panel