

Niemann-Pick Disease (Type A and B): *SMPD1* Gene Sequencing

Test Code: BY

Turnaround time: 4 weeks

CPT Codes: 81479 x1

Condition Description

Niemann-Pick Disease (NPD) is a lysosomal storage disorder resulting from the deficiency of the enzyme acid sphingomyelinase. This enzyme is needed to break down sphingomyelin, a lipid in the body. When insufficient enzyme is available, the sphingomyelin accumulates within the lysosomes. This accumulation of sphingomyelin interferes with cell function, eventually leading to damage in cells, tissues, and organs.

NPD can be classified into 3 different clinical forms, depending on the level of enzyme activity. Niemann-Pick disease, Type A (NPD-A), which accounts for roughly 2/3 of NPD, typically has the lowest level of enzyme activity. NPD-A is a progressive, neurodegenerative disease that presents in the first few months of life with hepatosplenomegaly and moderate lymphadenopathy. Neurologic symptoms include hypotonia and muscle weakness leading to feeding difficulties. In a recent natural history report the average age at diagnosis was 6 months of age [1].

Developmental milestones did not progress beyond 12 months of age, with no patients independently sitting, and subsequent regression of skills. Recurrent vomiting, constipation and diarrhea occur and may lead to growth delay and failure to thrive. Patients developed progressive elevations in liver enzymes. Ophthalmologic evaluation shows cherry red macula in all patients by age 12 months. The median time of survival from diagnosis was 21 months, and children rarely survive beyond three years of age.

Niemann-Pick disease, Type B (NPD-B), is more variable and the severity depends on the amount of active acid sphingomyelinase enzyme. NPD-B is characterized by visceral involvement only and survival into adulthood.

Classic NPD-B is a milder, more variable, non-neurodegenerative form with onset of symptoms in childhood or adolescence. Patients have involvement of the spleen, liver, and lungs, but typically do not have neurologic manifestations. Children may present with hepatosplenomegaly or hematologic abnormalities (such as elevated LDL cholesterol, triglycerides, low HDL, or low platelets). Some children experience growth delay. Pulmonary infiltration may be progressive with age and pulmonary infections are common. Intelligence is typically normal. Neurologic involvement is unusual in classic type B patients, but more common in patients with intermediate levels of active enzyme (so-called type A/B variant patients) and may include ataxia in patients of older adult ages. The enzymatic activity in these individuals is more variable, correlating with the milder presentation.

NPD is an autosomal recessive disorder due to mutations in the sphingomyelin phosphodiesterase-1 gene (*SMPD1*) which encodes acid sphingomyelinase. Missense mutations that produce an enzyme with reduced, but residual, catalytic activity are associated with NPD-B [2]. For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available.

For questions about testing for NPD, please call EGL Genetics at (404)778-8500 or (800)366-1502. For more information about lysosomal storage diseases, including management and treatment, please call Emory Lysosomal Storage Disease Center at (404)778-8565 or (800)200-1524.

References:

1. McGovern et al., Natural history of Type A Niemann-Pick disease: possible endpoints for therapeutic trials. 2006 *Neurology* 66: 228-232.
2. Ricci, V et al. Screening of 25 Italian patients with Niemann-Pick a reveals fourteen new mutations, one common and thirteen private, in *SMPD1*. 2004. *Hum. Mutat.* 24: 105.
3. Simonaro, et al. The Demographics and Distribution of Type B Niemann-Pick Disease: Novel Mutations Lead to New Genotype/Phenotype Correlations. 2002. *Am. Hum. Genet.* 71: 1413-1419.

Genes

[SMPD1](#)

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Niemann-Pick disease, Type A or B.
- Prenatal testing for known familial mutations.
- Assessment of carrier status in high risk family members through known mutation analysis.

Methodology

PCR amplification of 6 exons contained in the *SMPD1* gene coding region will be 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.

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Detection

Clinical Sensitivity:

For NPD-A, Ricci et al. identified 49 mutations out of 50 alleles in 25 individuals with NPD-A giving a detection rate of 98% [2]. Simonaro et al. identified 324 mutations in 228 individuals (456 alleles) with NPD-B, giving a detection rate of 71% [3].

Analytical Sensitivity: ~99%.

Specimen Requirements

Submit only 1 of the following specimen types

Type: Saliva**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: Whole Blood (EDTA)**Specimen Requirements:**

EDTA (Purple Top)

Infants and Young Children (2 years of age to 10 years old: 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: DNA, Isolated**Specimen Requirements:**

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Special Instructions

Please submit copies of diagnostic biochemical test results along with the sample. Contact the laboratory if further information is needed. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Mucopolysaccharide Screen (Urine GAG) (GA)
- Lysosomal Enzyme Screening Panel (LS)
- Known Mutation Analysis (KM) is available to test family members.
- Deletion/Duplication Assay is available separately for individuals where mutations are not identified by sequence analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.