Niemann-Pick Disease (Type A and B): \textit{SMPD1} Gene Deletion/Duplication

**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 (\textit{SMPD1}) which encodes acid sphingomyelinase. Missense mutations that produce an enzyme with reduced, but residual, catalytic activity are associated with NPD-B [2]. For questions about testing for NPD, call EGL Genetics at (470) 378-2200 or 855-831-7447. For further clinical information about lysosomal storage diseases, including management and treatment, call the Emory Lysosomal Storage Disease Center at (404) 778-8565 or (800) 200-1524.

**References:**

**Genes**

\textit{SMPD1}

**Indications**

- 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 known mutation analysis.

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region. Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**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: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

### Special Instructions

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

### Related Tests

- Mucopolysaccharide Screen (Urine GAG) (GA)
- Lysosomal Enzyme Screening Panel (LS)
- Known Mutation Analysis (KM) is available to test family members.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor for specific requirements for prenatal testing before collecting a fetal sample.