

Niemann-Pick Disease Type C2 via NPC2 Gene Sequencing--Test #474

Brief Description of Clinical Features: Niemann-Pick disease Type C (NPC) is a storage lipid disorder in which defects in the intracellular transport and trafficking of low-density lipoprotein (LDL)-derived cholesterol result in the accumulation of cholesterol and other lipids in tissues. NPC is characterized by an extensive clinical heterogeneity with regards to the age of onset, initial symptoms, severity, and progression. NPC can present at any time from intrauterine to the sixth decade with liver failure, incidental organomegaly, or a wide variety of neurological and psychiatric symptoms. Most common clinical features include enlarged spleen and liver, jaundice, dystonia, seizures, tremor, ataxia, vertical supranuclear gaze palsy, learning difficulty and slurred speech (Patterson, Neurologist 9:301-310, 2003; Vanier and Millat Clin Genet 64:269-281, 2003). Cases with fetal onset, detected ultrasonically in the form of severe ascites, were reported (Maconochie et al. Arch Dis Child 64:1391-1393, 1989; Manning et al. Arch Dis Child 65:335-336, 1990; Spiegel et al. Am J Med Genet 149A:446-450, 2009). NPC occurs worldwide; it is however more common in two genetic isolates. The first isolate is French originating from Normandy and settling in Nova Scotia (Millat et al. Am J Hum Genet 65:1321-1329, 1999); the second is Hispanic originating from the Upper Rio Grande Valley in the US and settling in New Mexico and Colorado (Wenger et al. Am J Dis Child 131:955-961, 1977). See also (Patterson, 2008, www.genetests.org).

Genetics: NPC is inherited with an autosomal recessive manner and is further divided into two subtypes, NPC1 and NPC2, on the basis of the causative gene. Clinically, NPC1 and NPC2 are identical. NPC2 (OMIM 607625) is caused by mutations in the NPC2 gene (Naurecki et al. Science 290:2298-2301, 2000). To date, ~18 different mutations have been reported in patients with variable ethnic background. Mutations included missense, nonsense, frameshift, small insertions and splicing.

Description of This Particular Test: The NPC2 gene encodes a soluble lysosomal protein with cholesterol binding properties; it is required for the egress of lipids from the lysosomes. This test involves bidirectional DNA sequencing of all 5 exons and splice sites of the NPC2 gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. We will sequence any single or double exons in family members of patients with known mutation or to confirm previous results.

Reference Sequences: Genomic: NC_000014.7 mRNA and Protein: CCDS: 32121.1

Indications for Test: Patients with clinical features suggestive of NPC and with no mutations in the NPC1 gene. Candidates for this test may include: (1) Patients with unexplained dementia or psychiatric illness and cognitive impairment, particularly when accompanied by ataxia, dystonia, or vertical supranuclear gaze palsy, (2) infants with unexplained cholestatic jaundice, and (3) older children with progressive liver disease (Patterson, Neurologist 9:301-310, 2003).

Sensitivity of Test: This test detects nearly 100 % of NPC2 sequence variants (Patterson, 2008, www.genetests.org), which are responsible for ~ 4 % of individuals with NPC (Park et al. Hum Mutat 22:313-325, 2003).

Turn Around Time: Maximum of 40 calendar days, although many tests are completed in 20-30 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of all coding exons of the NPC2 Gene: \$ 490

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 5	83898 \$ 120	Sequencing x 5	83904 \$ 190
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$ 70

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

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