

NPC1 and NPC2 / HE1 Gene Analysis in Niemann - Pick Disease, Type C

Clinical Features:

Niemann-Pick Disease Type C (NPC) is a rare lipid storage disorder that is characterized by accumulation of LDL-derived cholesterol in lysosomes. This abnormality leads to progressive neurological deterioration, visceral symptoms and premature death. Neurologic abnormalities gradually develop, including ataxia, spasticity, seizures, dysarthria and dysphagia. Other features presenting later in life may include dystonia and vertical supranuclear gaze palsy, dementia and psychiatric manifestations. Hepatomegaly and/or splenomegaly may or may not be present. The age and severity of onset can vary widely. The biochemical diagnosis can be made on cultured skin fibroblasts by evaluating LDL-derived cholesterol esterification and/or with filipin staining showing intracellular accumulation of cholesterol. Two genes are associated with NPC. Variants in the NPC1 and NPC2 genes result in similar clinical and biochemical phenotypes but can be distinguished by complementation group. NPC1 represents the major complementation group and is due to pathogenic variants in the NPC1 gene whereas NPC2 is caused by pathogenic variants in the NPC2/HE1 gene. Pathogenic variants in NPC1 are responsible for approximately 95% of Niemann-Pick Type C cases, while approximately 4-5% of patients have pathogenic variants in the NPC2/HE1 gene.^{1,2}

Genetics:

Niemann-Pick Disease Type C (NPC) has an autosomal recessive pattern of inheritance.

Test Methods:

Sequencing of the NPC1 and NPC2/HE1 genes are offered. Using genomic DNA obtained from the submitted specimen, bi-directional sequence of the coding region and splice junctions of the NPC1 gene (exons 1-25) or NPC2/HE1 gene (exons 1-5) are analyzed. If sequencing identifies a variant on only one allele of NPC1 or NPC2/HE1, focused array CGH analysis with exon-level resolution (ExonArrayDx) will be performed to evaluate for a deletion or duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:

In 143 unrelated patients diagnosed with Niemann-Pick Type C by abnormal filipin staining and absent or decreased cholesterol esterification in fibroblasts, approximately 80% had two variants in the NPC1 gene and 7% had a single variant in NPC1.² In addition, five patients were identified with two variants identified in the NPC2/HE1 gene, and one patient was found to harbor a single NPC2/HE1 gene variant.² In another study of patients of the NPC2 group, variants were identified on 12/12 NPC2/HE1 alleles.³

Variant Spectrum:

Over 200 variants in the NPC1 gene have been reported. Approximately 70% are missense variants followed by nonsense, splice site, small deletions/insertions and a large deletion.^{1,2} Approximately one-third of variants in NPC1 involve a specific cysteine-rich domain positioned in a large extracellular loop.⁴ Most variants are private; however, three frequent NPC1 variants have been described including p.I1061T that accounts for approximately 20% of disease alleles in the United Kingdom and France and 15% in the United States.¹ The two other recurrent variants are p.P1007A, frequent in Europe, and p.G992W, found in patients from Nova-Scotia.¹ To date, 17 variants have been described in the NPC2/HE1 gene, the majority of which are missense/nonsense, followed by splice site and small deletions. The most common variant in NPC2/HE1 is a nonsense variant, p.E20X, which occurs on approximately 50% of disease alleles.² Some degree of genotype/phenotype correlation has been reported for both the NPC1 and NPC2/HE1 genes.^{1,2,4,5}

References:

1. Millat et al., (2005) Mol Genet Metab 86:220-232
2. Park et al., (2003) Hum Mut 22:313
3. Verot et al., (2007) Clin Genet 71:320-30
4. Sevin et al., (2007) Brain 130:120-133
5. Fernandez-Valero et al., (2005) Clin Genet 68 :245-254.