NPC1 and NPC2 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 be present. The onset age and severity can vary widely.

Genetics:
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* 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* gene.[1,2] 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.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Sequencing of the *NPC1* and *NPC2* genes is 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* gene (exons 1-5) are analyzed. If clinically indicated, for patients who have a single variant identified after full sequencing of both the *NPC1* and *NPC2* genes, GeneDx will perform reflex deletion/duplication testing (ExonArrayDx) at no additional charge. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing 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* gene, and one patient was found to

harbor a single *NPC2* gene variant.[2] In another study of patients of the NPC2 group, variants were identified on 12/12 *NPC2* alleles.[3] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

Over 450 variants in the *NPC1* gene have been reported. Approximately 60% are missense variants followed by nonsense, splice site, small deletions/insertions and large deletions.[1,2,6] 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, 27 variants have been described in the *NPC2* gene, the majority of which are misssense/nonsense, followed by splice site and small deletions.[6] The most common variant in *NPC2* 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* genes.[1,2,4,5]

References:

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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.
6. Stenson et al., (2014) Hum Genet 133 (1):1-9