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 evaluation of LDL-derived cholesterol esterification or filipin staining in cultured skin fibroblasts, or plasma oxysterol profile may be helpful in the diagnosis when variants of uncertain significance identified by molecular testing. [6, 7, 8]

INHERITANCE PATTERN

Autosomal Recessive

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the NPC1 and/or NPC2 genes are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request. Testing for the NPC1 and NPC2 genes can be ordered sequentially, if specifically requested, or both genes can be analyzed simultaneously if a more rapid turnaround time is needed.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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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.[1,2,9] 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 NPC2gene, the majority of which are missense/nonsense, followed by splice site and small deletions.[9] 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 NPC2genes.[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
6. Patterson (2020) [Updated 2020 Dec10]. In: Adam, MP, Ardinger HH, Pagon RA et al., Eds. Gene Reviews. [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1296/
7. Porter et al., (2010) Sci Transl Med 2(56)56ra81
8. Reunert et al.,(2016) E BioMedicine 4:170-175
9. Stenson et al., (2014) Hum Genet 133 (1)