TPP1 Gene Analysis in Neuronal Ceroid-Lipofuscinosis 2 (CLN2)

Clinical Features:
The neuronal ceroid-lipofuscinoses are a group of inherited, neurodegenerative, lysosomal storage disorders that are associated with variants in at least 13 genes. Variants in the TPP1 (CLN2) gene are most commonly associated with the classic late-infantile neuronal ceroid-lipofuscinosis (LINCL) form that is characterized by onset of symptoms between 2 and 4 years. Epilepsy is typically the presenting symptom followed by regression of developmental milestones: speech delay, slow learning, intellectual disability, dementia, and neuromotor dysfunction including ataxia and the inability to walk are characteristic. Visual impairment typically appears at age 4 to 6 years, with rapid progression to blindness. Life expectancy of the more common classic late infantile form ranges from 6 years to early teens. Some patients with variants in the TPP1 gene have been reported with juvenile neuronal ceroid-lipofuscinosis (JNCL) presentation that is characterized by later onset with the presenting symptom being visual impairment, followed by epilepsy. As a group the neuronal ceroid-lipofuscinoses are the most common hereditary progressive neurodegenerative disease with an incidence ranging from 1 to 7 per 100,000 births.

Genetics:
LINCL and variant JNCL may be caused by variants in the TPP1 (CLN2) gene that encodes the lysosomal tripeptidyl-peptidase 1 (TPP1) enzyme that sequentially removes N-terminal tripeptides from small peptides, including several peptide hormones. Deficiency of the TPP1 enzyme results in accumulation of ATP synthase subunit C in neuronal cells. TPP1 enzyme assay is used for diagnosis or confirmation, although curvilinear profiled can be observed by electron microscopy in fibroblasts or lymphocytes. The TPP1 gene is located on chromosome 11p15 and has 13 exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the TPP1 gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNVC). 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.

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.

Variant Spectrum:
At this time, greater than 150 variants in the *TPP1* gene have been reported and include missense, nonsense, splice site, small deletions/insertions, gross deletions, and frameshift. Two variants are most commonly observed, c.509-1 G>C and p.Arg208X, and account for 50% of disease-associated alleles. A well-established founder mutation includes c.851 G>T (p.Gly248Val), reported as the second most common allele in North America associated with LINCL. A p.Arg447His variant appears to be associated with protracted LINCL; however, for the most part genotype/phenotype correlations are not well established.

References: