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.[1] Life expectancy of the more common classic late infantile form ranges from 6 years to early teens.[1] 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.[1] 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.[1]

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.[1] Deficiency of the TPP1 enzyme results in accumulation of ATP synthase subunit C in neuronal cells.[2] 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:
Variant analysis of the *TPP1* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *TPP1* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/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 48 patients with LINCL or JNCL and deficient TPP1 enzyme activity, sequence analysis of the *TPP1* gene identified variants on approximately 95% of alleles (91/96).[3] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

At this time, greater than 100 variants in the *TPP1* gene have been reported and include missense, nonsense, spice site, small deletions/insertions and frameshift. Two variants are most commonly observed, c.509-1 G>C and p.Arg208X, accounting for approximately 44-60% of mutant alleles in patients with LINCL.[3, 4] A p.Arg447His variant appears to be associated with protracted LINCL; however, for the most part genotype/phenotype correlations are not well established.[3]

References:

1. Mole, S. and Williams, R. (Updated [Aug 1 2013]) Neuronal Ceroid-Lipofuscinoses. In: GeneReviews at Genetests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2011. Available at http://www.genetests.org.
2. Hofmann et al., (2002) Curr Mol Med 2:423-437.
3. Sleat et al., (1999) Am J Hum Genet 64:1511-1523.