

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 eight 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 ranges from 6 years to older than 40 years.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:

Autosomal Recessive

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 Electron microscopy of patient tissues shows the presence of predominately curvilinear storage bodies (CB) or CB combined with fingerprint (FP) profiles, which consist of lipofuscin storage material a major component of which is mitochondrial ATP synthase subunit C.. The TPP1 gene is located on chromosome 11p15 and has 13 exons.

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

References:

1. Mole, S. and Williams, R. (Updated [March 2, 2010]) 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.
4. Zhong et al., (2000) *Genet Med* 2:312-318.