Test Definition: TPPTL

TPP1 and PPT1, WBC

Overview

Useful For

Evaluation of patients with clinical presentations suggestive of neuronal ceroid lipofuscinoses (NCL)

Aids in the differential diagnosis of infantile and late infantile NCL

This test is **not useful for** detecting carrier status of NCL.

Genetics Test Information

This blood test is an appropriate first step for individuals between 0 and 4 years of age who present with symptoms consistent with neuronal ceroid lipofuscinosis.

Special Instructions

- Informed Consent for Genetic Testing
- Biochemical Genetics Patient Information
- Informed Consent for Genetic Testing (Spanish)

Method Name

Fluorometric

NY State Available

Yes

Specimen

Specimen Type

Whole Blood ACD

Shipping Instructions

For optimal isolation of leukocytes, it is recommended the specimen arrive refrigerated within 6 days of collection to be stabilized. Collect specimen Monday through Thursday only and not the day before a holiday. Specimen should be collected and packaged as close to shipping time as possible.

Specimen Required

Container/Tube:

Preferred: Yellow top (ACD solution B)

Acceptable: Yellow top (ACD solution A)

Specimen Volume: 6 mL

Collection Instructions: Send specimen in original tube. **Do not aliquot**.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Biochemical Genetics Patient Information (T602) in Special Instructions

3. If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request (T798) with the specimen.

Specimen Minimum Volume

5 mL

Reject Due To

Gross hemolysis	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood ACD	Refrigerated (preferred)	6 days	YELLOW TOP/ACD
	Ambient	6 days	YELLOW TOP/ACD

Clinical and Interpretive

Clinical Information

The neuronal ceroid lipofuscinoses (NCL) comprise a group of recessively inherited neurodegenerative disorders involved in lysosomal protein catabolism. They are considered the most common of the neurogenetic storage disorders, with incidences ranging from 1.3 to 7 per 100,000 live births. Clinically, they are characterized by vision loss, seizures, mental regression, behavioral changes, movement disorders, and the accumulation of autofluorescent storage material in the brain and tissues. Although at least 12 different genes have been identified, the NCL have traditionally been categorized based on the age of onset of symptoms: infantile, late-infantile, juvenile, and adult. Infantile and late-infantile NCL are caused primarily by defects in *PPT1* and *TPP1,* respectively. Tissue damage is selective for the nervous system and many patients die in the first decade of life due to central nervous system degeneration.

Children affected by infantile NCL (CLN1) typically have normal growth and development until about 6 to 12 months of age. Slowed head growth occurs at around 9 months followed by psychomotor degeneration, seizures, and progressive macular degeneration leading to blindness by the age 2 years. CLN1 is caused by a deficiency of the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which cleaves long-chain fatty acids (usually palmitate) from cysteine residues. Electron microscopy shows granular osmophilic deposits in most cell types. PPT1 is thought to play an active role in various cell processes including apoptosis, endocytosis, and lipid metabolism. Infantile NCL has an incidence of 1 in 20,000 in Finland and is rare elsewhere.

The late infantile form of NCL (CLN2) is primarily caused by deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), which cleaves tripeptides from the N-terminus of polypeptides. Tissue damage results from the defective degradation and consequent accumulation of storage material with a curvilinear profile by electron microscopy. There is widespread loss of neuronal tissue especially in the cerebellum and hippocampal region. Disease onset occurs at 2 to 4 years of age with seizures, ataxia, myoclonus, psychomotor retardation, vision loss, and speech

impairment.

Diagnostic strategy depends on the age of onset of symptoms. In children presenting between the ages 0 to 4 years, enzyme assay of PPT1 and TPP1 is an appropriate first step. For other patients suspected of having an NCL, the molecular genetic test is available; see NCLGP / Neuronal Ceroid Lipofuscinosis (Batten Disease) Gene Panel, Varies.

Reference Values

TRIPEPTIDYL PEPTIDASE 1

85-326 nmol/hour/mg protein

PALMITOYL-PROTEIN THIOESTERASE 1

20-93 nmol/hour/mg protein

Interpretation

Tripeptidyl peptidase 1 (TPP1) enzyme activity or palmitoyl-protein thioesterase 1 (PPT1) enzyme activity below 5 nmol/hour/mg of protein is highly suggestive of late-infantile and infantile neuronal ceroid lipofuscinoses (NCL), respectively.

Cautions

Some variants with an age of onset occurring in older individuals have been noted.

Clinical Reference

1. Mole S, Cotman S: Genetics of the neuronal ceroid lipofuscinoses (Batten disease). Biochem et Biophys Acta. 2015 Oct;1852:2237-2241

2. Kavianen R, Eriksson K, Losekoot M, et al: Juvenile-onset neuronal ceroid lipofuscinosis with infantile CLN1 mutation and palmitoyl-protein thioesterase deficiency. Eur J Neurol. 2007 Apr;14(4):369-372

3.Giugliani R, Vairo F, Beck M, et al: Lysosomal disorders. In: Sarafoglou K, Hoffman GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed. McGraw-Hill Medical Division; 2017:983-1021

4. Nita DA, Mole SE, Minassian BA: Neuronal ceroid lipofuscinoses. Epileptic Disord. 2016 Sep 1;18(S2):73-88. doi: 10.1684/epd.2016.0844

5. Williams RE, Adams HR, Blohm M, et al: Management strategies for CLN2 disease. Pediatr Neurol. 2017 Apr;69:102-112. doi: 10.1016/j.pediatrneurol.2017.01.034

6. Mole SE, Anderson G, Band HA, et al: Clinical challenges and future therapeutic approaches for neuronal ceroid lipofuscinosis. Lancet Neurol. 2019 Jan;18(1):107-116. doi: 10.1016/S1474-4422(18)30368-5

Performance

Method Description

The synthetic substrate for palmitoyl-protein thioesterase 1 (PPT1) is 4-methylumbelliferyl-6-thiopalmitoyl-beta-glucoside. The leukocytes are homogenized and combined with protein and a substrate and incubated. The reaction is stopped with a glycine buffer. The fluorescence of the 4-methylumbelliferone product is read using a fluorescence plate reader and activity is calculated based on amount of product formed during the 1-hour incubation period.(van Diggelen OP, Keulemans JL, Winchester B, et al: A rapid fluorogenic palmitoyl-protein thioesterase assay: pre and

postnatal diagnosis of INCL. Mol Genet Metab. 1999 Apr;66(4):240-244; Cowan T, Pasquali M: Laboratory investigations of inborn errors of metabolism. In: Sarafoglou K, Hoffman GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed. McGraw-Hill; 2017:1139-1158)

The synthetic substrate for tripeptidyl peptidase 1 (TPP1) is Ala-Ala-Phe-7-amido-4-methylcoumarin. The leukocytes are homogenized and combined with protein and a substrate and incubated. The reaction is stopped with a glycine buffer. The fluorescence of the 7-amino-4-methylcoumarin product is read using a fluorescence plate reader and activity is calculated based on amount of product formed during the 1-hour incubation period.(Sohar I, Lin L, Lobel P: Enzyme-based diagnosis of classical late infantile neuronal ceroid lipofuscinosis: comparison of tripeptidyl peptidase I and pepstatin-insensitive protease assays. Clin Chem. 2000 Jul;46(7):1005-1008; Cowan T, Pasquali M: Laboratory investigations of inborn errors of metabolism. In: Sarafoglou K, Hoffman GF, Roth KS, eds. Pediatric Endocrinology and Inborn Errors of Metabolism. 2nd ed. McGraw-Hill; 2017:1139-1158)

PDF Report

No

Day(s) Performed

Preanalytical processing: Monday through Saturday.

Assay performed: Twice per month

Report Available

8 to 15 days

Specimen Retention Time

WBC homogenate: 1 month

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

82657

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
TPPTL	TPP1 and PPT1, WBC	93704-5

Test Definition: TPPTL

TPP1 and PPT1, WBC

Result ID	Test Result Name	Result LOINC Value
50688	Specimen	31208-2
50689	Specimen ID	57723-9
50690	Source	31208-2
50691	Order Date	82785-7
50692	Reason for Referral	42349-1
50693	Method	85069-3
50694	TPP1L	76038-9
50695	PPT1L	74935-8
50696	Interpretation	59462-2
50697	Amendment	48767-8
50698	Reviewed By	18771-6
50699	Release Date	82772-5