Test Definition: BTDZ

Biotinidase Deficiency, BTD Full Gene Analysis, Varies

Overview

Useful For

Second-tier test for confirming biotinidase deficiency (indicated by biochemical testing or newborn screening)

Carrier testing of individuals with a family history of biotinidase deficiency, but disease-causing mutations have not been identified in an affected individual

Testing Algorithm

Amplification and DNA sequencing are utilized to test for the presence of a mutation in the *BTD* gene.

Special Instructions

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

Method Name

Polymerase Chain Reaction (PCR) Amplification/DNA Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of draw.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.
Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.

2. Send specimen in original tube.

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. Molecular Genetics: Biochemical Disorders Patient Information (T527) in Special Instructions
3. If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request (T798) with the specimen.

Specimen Minimum Volume

0.5 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Refrigerated		
	Frozen		

Clinical & Interpretive

Clinical Information

Biotinidase deficiency is an inherited metabolic disease caused by reduced levels of biotinidase, an enzyme that recycles biotin by releasing it from its metabolic product, biocytin, or exogenous dietary proteins. Biotin is a vitamin that serves as a coenzyme for 4 carboxylases that are essential for amino acid catabolism, gluconeogenesis, and fatty acid synthesis. Depletion of free biotin reduces carboxylase activity, resulting in secondary carboxylase deficiency. Depending on the amount of residual biotinidase activity, individuals can have either profound or partial biotinidase deficiency. Age of onset and clinical phenotype vary among individuals. Profound biotinidase deficiency occurs in approximately 1 in 137,000 live births and partial biotinidase deficiency occurs in approximately 1 in 110,000 live births, resulting in a combined incidence of about 1 in 61,000.

Untreated profound biotinidase deficiency (<10% of normal biotinidase activity) manifests within the first decade of life as seizures, hypotonia, neurosensory hearing loss, respiratory problems, and cutaneous symptoms including skin rash, alopecia, and recurrent viral or fungal infections. Among children and adolescents with profound biotinidase deficiency, clinical features include ataxia, sensorineural hearing loss, developmental delay, and eye problems such as optic neuropathy leading to blindness. Partial biotinidase deficiency (10%-30% of normal biotinidase activity) is associated with a milder clinical presentation, which may include cutaneous symptoms without neurologic involvement.

Treatment with biotin has been successful in both preventing and reversing the clinical features associated with

biotinidase deficiency. As a result, biotinidase deficiency is included in most newborn screening programs in order to prevent disease. Biotinidase deficiency exhibits a similar clinical presentation to carboxylase and holocarboxylase synthetase deficiency. Therefore, measurement of the biotinidase enzyme is required to differentiate between these diseases and ensure proper diagnosis. Newborn screening for biotinidase deficiency involves direct analysis of the biotinidase enzyme from blood spots obtained shortly after birth. This enables early identification of potentially affected individuals and quick follow-up with confirmatory biochemical and molecular testing.

Biotinidase deficiency is inherited in an autosomal recessive manner, caused by mutations in the biotinidase gene (*BTD*). The carrier frequency for biotinidase deficiency in the general population is about 1:120. Several common mutations in the *BTD* gene have been identified, accounting for about 60% of affected individuals. Sequencing of the entire *BTD* gene detects other, less common, disease-causing mutations. While genotype-phenotype correlations are not well established, it appears that certain mutations are associated with profound biotinidase deficiency, while others are associated with partial deficiency.

The recommended first-tier test to screen for biotinidase deficiency is a biochemical test that measures biotinidase enzyme activity, either newborn screening or BIOTS / Biotinidase, Serum. Molecular tests form the basis of confirmatory or carrier testing. Individuals with decreased enzyme activity are more likely to have 2 identifiable mutations in the *BTD* gene by molecular genetic testing.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

A small percentage of individuals who are carriers or have a diagnosis of biotinidase deficiency may have a mutation that is not identified by this method (eg, large genomic deletions, promoter mutations). The absence of a mutation, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of biotinidase deficiency. For carrier testing, it is important to first document the presence of a *BTD* gene mutation in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424

2. Kaye CI, Committee on Genetics, Accurso F, et al: Newborn screening fact sheets. Pediatrics 2006 Sep;118(3):e934-963
3. Moslinger D, Muhl A, Suormala T, et al: Molecular characterization and neuropsychological outcome of 21 patients with profound biotinidase deficiency detected by newborn screening and family studies. Eur J Pediatr 2003 Dec;162 Suppl 1:S46-49 Epub 2003 Nov 20
4. Nyhan WL, Barshop B, Ozand PT: Multiple carboxylase deficiency/biotinidase deficiency. In Altas of Metabolic Diseases. Second edition. New York, Oxford University Press, 2005 pp 42-48
5. Wolf B, Jensen KP, Barshop B, et al: Biotinidase deficiency: novel mutations and their biochemical and clinical correlates. Hum Mutat 2005 Apr;25(4):413

Performance

Method Description
Bi-directional sequence analysis is performed to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *BTD* gene.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Varies

Report Available
14 to 20 days

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81404-*BTD* (biotinidase) (eg, biotinidase deficiency), full gene sequence

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
BTDZ	BTD Gene, Full Gene Analysis	94242-5

Result ID	Test Result Name	Result LOINC® Value
53463	Result Summary	50397-9
53464	Result	82939-0
53465	Interpretation	69047-9
53466	Additional Information	48767-8
53467	Specimen	31208-2
53468	Source	31208-2
53469	Released By	18771-6