Biotinidase Deficiency (BTD) Sequencing

Biotinidase deficiency (BTD), a disorder that affects approximately 1 in 60,000 individuals, is caused by biallelic pathogenic variants in the *BTD* gene.[1] Specific variants are associated with the degree of deficiency, either partial or profound. Molecular testing of the *BTD* gene may be useful if enzymatic testing suggests BTD.

Deficiency in biotinidase enzymatic activity impairs the body's ability to recycle and reuse the vitamin biotin, resulting primarily in neurologic and dermatologic manifestations.[2,3] Timely diagnosis is important. Early identification and treatment of BTD can prevent and even reverse some symptoms, whereas untreated BTD may result in permanent neurologic, visual, and hearing impairment.[2,4] Refer to the ARUP Consult Biotinidase Deficiency topic for additional information about screening and laboratory testing for this condition.

Tests to Consider

Biotinidase Deficiency (BTD) Sequencing 0051730

Method: Polymerase Chain Reaction/Sequencing

Molecular DNA test to confirm a diagnosis of BTD when biotinidase enzymatic activity is low

Related Tests

Biotinidase, Serum (with Paired Normal Control) 0093362

Method: Spectrophotometry

Initial biotinidase enzyme test to diagnose or rule out BTD

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Recommended test for a known familial sequence variant previously identified in a family member

Disease Overview

Incidence

- Carrier frequency: 1/120[5]
- Variants confer[5]:
  - Profound BTD in 1/~137,000
  - Partial BTD in 1/~110,000
  - Profound and partial BTD (combined incidence) in 1/~61,000

Symptoms

- Profound BTD (<10% of normal biotinidase activity)[3]
  - Seizures
  - Developmental delay
  - Hypotonia
  - Ataxia
  - Vision problems
  - Hearing loss
  - Alopecia
  - Rashes
- Partial BTD (10-30% of normal biotinidase activity)[3]
  - Mild forms of symptoms associated with profound BTD may manifest under stress (eg, surgery or infection)[5]

Screening

- Newborn screening for BTD is performed across the United States.[3]
- Confirmatory testing following an abnormal newborn screen includes evaluation of enzyme activity in serum and may include molecular testing of the *BTD* gene.[3]

Refer to the American College of Medical Genetics and Genomics Biotinidase Deficiency algorithm for more information.[6]

Genetics

Gene

BTD

Inheritance

Autosomal recessive

Variants

More than 200 different variants have been identified in the *BTD* gene.[7]

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity: 99%
- Analytical sensitivity/specificity: 99%

Results

Variant(s) Detected[a]	Clinical Significance
2 pathogenic *BTD* gene variants identified on opposite chromosomes	Predicts a diagnosis of BTD
1 severe and 1 mild *BTD* gene variant identified	Predicts partial BTD
1 copy of a pathogenic *BTD* gene variant identified	Predicts that individual is at least a carrier of BTD
No pathogenic gene variants detected by sequencing	Likelihood is reduced that the individual is a carrier of or affected by BTD

[a]The variant database hosted by ARUP Laboratories[7] is a helpful resource that includes information about more than 200 variants that affect biotinidase.

Limitations

- Variants of unknown clinical significance may be identified.
- Does not detect:
  - Large deletions or duplications
  - Deep intronic or regulatory region variants
- Diagnostic errors can occur due to rare sequence variations.

References

1. National Organization for Rare Disorders (NORD). Rare Disease Database: Biotinidase deficiency. [Published: 2019; Accessed: Feb 2021]
2. Hayek W, Dumin Y, Tal G, et al. Biotinidase deficiency: a treatable neurological inborn error of metabolism. Isr Med Assoc J. 2019;21(3):219-221. PubMed
3. Strovel ET, Cowan TM, Scott AI, et al. Laboratory diagnosis of biotinidase deficiency, 2017 update: a technical standard and guideline of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(10). PubMed
4. Wolf B. Biotinidase deficiency should be considered in individuals thought to have multiple sclerosis and related disorders. Mult Scler Relat Disord. 2019;28:26-30. PubMed
5. Wolf B. Biotinidase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2021. [Updated Jun 2016; Accessed: Feb 2021]
6. American College of Medical Genetics and Genomics. Biotinidase deficiency [algorithm]. [Published: 2006; Accessed: Feb 2021]
7. ARUP Laboratories, University of Utah Health. BTD database. [Accessed: Feb 2021]