

# Biotinidase Deficiency (*BTD*)

## *TO CONFIRM A DIAGNOSIS OR CARRIER STATUS OF BIOTINIDASE DEFICIENCY BY DNA*

### Disease Overview

- Biotinidase is necessary for recycling biotin (a vitamin).
- Profound biotinidase deficiency (less than 10 percent of normal biotinidase activity) is characterized by seizures, developmental delay, hypotonia, ataxia, visual problems, hearing loss, alopecia, rashes, and candidiasis.
- Partial biotinidase deficiency (10–30 percent of normal biotinidase activity) may cause hypotonia, rashes, and alopecia, especially in time of stress (i.e., prolonged infection).
- Enzymatic newborn screening usually detects both partial and profound biotinidase deficiency
- Follow-up testing of biotinidase enzyme activity in serum should be performed to confirm all positive newborn screens.
- Affected individuals develop normally if treated daily with 5–10 mg of biotin orally before symptoms occur.

### Epidemiology

- Profound biotinidase deficiency: one in 137,000.
- Partial biotinidase deficiency: one in 109,000.
- Profound or partial biotinidase deficiency: one in 60,000.
- Carrier frequency: one in 120.

### Genetics

- Biotinidase deficiency is autosomal recessive.
- The *BTD* gene has four exons.
- More than 100 different mutations have been identified in the *BTD* gene.
- A panel of five common *BTD* mutations detects 60 percent of mutant alleles.
- The most common severe mutations in *BTD* are G93del7ins3 (occurring in 50 percent of affected individuals) and p.R538C.
- p.Q456H and the double mutation p.A171T:D444H are also common severe mutations.
- By itself, the p.D444H mutation reduces enzymatic function by 50 percent and is therefore considered a mild mutation. When p.D444H is combined with a severe mutation on the opposite allele, partial biotinidase deficiency results.

### Indications for Ordering

- Biotinidase Deficiency (*BTD*) Sequencing
  - Positive newborn screen for biotinidase deficiency.
  - To determine the *BTD* mutations when *BTD* enzymatic activity is low.
  - Testing for carrier status in relatives of affected patients when the familial mutations are not known.
- Biotinidase Deficiency (*BTD*) 5 Mutations
  - Testing for affected or carrier status in relatives of affected patients when the familial mutations are included in the five mutations tested.

### Contraindications

- Biotinidase Deficiency (*BTD*) Sequencing
  - Prenatal testing.
  - Testing relatives of affected individuals when the causative mutation(s) are known. Call ARUP's genetic counselor to order custom sequencing for the specific *BTD* mutation(s).
- Biotinidase Deficiency (*BTD*) 5 Mutations
  - Testing when the specific mutations are not known to be included in the five tested.

### Additional Ordering Notes

- If the patient has had previous enzymatic testing for biotinidase deficiency, please provide the enzymatic value for the most accurate test interpretation.
- If there is a positive family history of biotinidase deficiency, please provide information regarding how the affected individual is related to the patient and the specific *BTD* mutations.

### Interpretation

- Identification of two *BTD* mutations on separate chromosomes is consistent with being affected with biotinidase deficiency.
- Identification of one severe and one mild *BTD* mutation predicts the presence of partial biotinidase deficiency.
- Identification of one *BTD* mutation predicts biotinidase deficiency carrier status.
- Lack of identification of a *BTD* mutation using the 5 mutation panel does not rule out carrier or affected status.
- Identification of no *BTD* mutations by sequencing predicts the individual is not likely to be a carrier of or affected with biotinidase deficiency.
- Novel *BTD* mutations of unknown clinical significance may be identified by sequencing.

### Methodology

- Biotinidase Deficiency (*BTD*) Sequencing
  - Bidirectional sequencing of all *BTD* coding regions and exon/intron borders.
  - Analytical sensitivity and specificity are 99 percent.
  - Clinical sensitivity is approximately 99 percent.
- Biotinidase Deficiency (*BTD*) 5 Mutations
  - Five common *BTD* gene mutations c. 98\_104d7i3 (G98del7ins3), c. 1368A>C (p.Q456H), c.1612C>T (p.R538C), c. 1330G>C (p.D444H), and c. 511G>A (p.A171T:D444H) are detected by polymerase chain reaction (PCR), single nucleotide extension (SNE), and fluorescent monitoring.
  - Analytical sensitivity and specificity are 99 percent.
  - Clinical sensitivity is approximately 60 percent.

### Limitations

- Biotinidase Deficiency (*BTD*) Sequencing
  - Rare large *BTD* gene deletions or duplications are not detectable.
  - Deep intronic mutations or those within the promoter will not be detected.
  - Analytic sensitivity may be compromised by rare primer-site mutations.
- Biotinidase Deficiency (*BTD*) 5 Mutations
  - *BTD* mutations, other than the five targeted, will not be detected.
  - Clinical sensitivity may be compromised by rare primer-site mutations.

### Related Test

- Biotinidase, Serum (with paired normal control) (0093362)
- Biotinidase Deficiency (*BTD*) Familial Mutation, Targeted Sequencing (2001961)

### References

1. Muhl A, et al. Molecular characterisation of 34 patients with biotinidase deficiency ascertained by newborn screening and family investigation. *Eur J Hum Gen* 2001; 9:237–43.
2. Pomponio RJ Mutations in the human biotinidase gene that cause profound biotinidase deficiency in symptomatic children: molecular, biochemical, and clinical analysis. *Pediatr Res* 1997; 42:840–8.

## Test Information

**0051700**      **Biotinidase Deficiency (*BTD*) 5 Mutations**  
**0051730**      **Biotinidase Deficiency (*BTD*) Sequencing**

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).