Biotinidase Deficiency (*BTD*)

Indications for Ordering

- Follow up positive newborn screen for biotinidase deficiency
- Identification of *BTD* gene variants when biotinidase enzymatic activity is low
- Carrier testing for relatives of affected individuals when familial variants are unknown

Test Description

Biotinidase Deficiency (*BTD*) Sequencing
- Bidirectional sequencing of all *BTD* coding regions and intron/exon borders

Biotinidase Deficiency (*BTD*) 5 Mutations
- c. 98_104del7ins3 (G98d7i3)
- c. 1368A>C (p.Q456H)
- c. 1612C>T (p.R538C)
- c. 1330G>C (p.D444H)
- c. 511G>A (p.A171T:D444H)
  - Polymerase chain reaction
  - Capillary electrophoresis

Tests to Consider

Typical testing strategy
- Biotinidase enzyme testing
  - Initial screening test for biotinidase deficiency
- Molecular testing for *BTD* gene variants
  - Use if enzymatic testing is suggestive of biotinidase deficiency

Primary tests

Biotinidase Deficiency (*BTD*) 5 Mutations 0051700
- Molecular DNA test to confirm a diagnosis of biotinidase deficiency when biotinidase enzymatic activity is low
- Carrier testing for individuals with a family history of biotinidase deficiency if familial variants are included in this test

Biotinidase Deficiency (*BTD*) Sequencing 0051730
- Molecular DNA test to confirm a diagnosis of biotinidase deficiency when biotinidase enzymatic activity is low

Related tests

Biotinidase, Serum (with Paired Normal Control) 0093362
- Initial biotinidase enzyme test to diagnose or rule out biotinidase deficiency

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence
- Profound biotinidase deficiency – 1/137,000
- Partial biotinidase deficiency – 1/110,000
- Profound or partial biotinidase deficiency – 1/61,000 newborns
- Carrier frequency – 1/120

Symptoms
- Profound biotinidase deficiency (<10% of normal biotinidase activity)
  - Seizures
  - Developmental delay
  - Hypotonia
  - Ataxia
  - Vision problems
  - Hearing loss
  - Alopecia
  - Rashes
  - Candidiasis
- Partial biotinidase deficiency (10-30% of normal biotinidase activity)
  - Hypotonia
  - Rashes
  - Alopecia, especially in time of stress (eg, prolonged infection)
- Affected individuals develop normally if treated daily with 5-10 mg of biotin orally before symptoms occur

Screening
- 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

Genetics

Gene – *BTD*

Inheritance – autosomal recessive

Variants

>100 different variants identified in *BTD* gene

- Five common variants
  - c. 98_104d7i3 (G98del7ins3)
    - Present in 50% of affected individuals
  - c. 1612C>T (p.R538C)
  - c. 1368A>C (p.Q456H)
  - c. 511G>A (p.A171T:D444H)
  - c. 1330G>C (p.D444H)
    - p.D444H only is considered a mild variant
    - Reduces enzymatic function by 50%
    - If combined with a severe variant on the opposite allele, a partial biotinidase deficiency results

Test Interpretation

Sensitivity/specificity

Biotinidase Deficiency (*BTD*) 5 Mutations

- Clinical sensitivity – 60%
- Analytical sensitivity/specificity – 99%

Biotinidase Deficiency (*BTD*) Sequencing

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

Results

- Two pathogenic *BTD* gene variants identified on opposite chromosomes
  - Predicts a diagnosis of biotinidase deficiency
- One severe and one mild *BTD* gene variant identified
  - Predicts partial biotinidase deficiency
- One copy of a pathogenic *BTD* gene variant identified
  - Predicts that individual is at least a carrier of biotinidase deficiency
- No pathogenic gene variants detected by sequencing
  - Likelihood is reduced that the individual is a carrier of or affected with biotinidase deficiency

Limitations

Biotinidase Deficiency (*BTD*) 5 Mutations

- *BTD* gene variants other than the 5 targeted will not be detected
- Lack of identification of a *BTD* gene variant using this test does not rule out carrier or affected status
- Diagnostic errors can occur due to rare sequence variations

Biotinidase Deficiency (*BTD*) Sequencing

- 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