Biotinidase Deficiency (BTD) Sequencing

Biallelic pathogenic variants in the \textit{BTD} gene are the cause of biotinidase deficiency (BTD), a disorder that affects approximately 1 in 60,000 individuals.\textsuperscript{1} Specific variants are associated with the degree of deficiency, partial or profound. Molecular testing of the \textit{BTD} gene may be useful if enzymatic testing suggests BTD.

The deficiency in biotinidase enzymatic activity impairs the body's ability to recycle and reuse the vitamin biotin, and results primarily in neurologic and dermatologic manifestations.\textsuperscript{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.\textsuperscript{2,4} Refer to the ARUP Consult \textit{Biotinidase Deficiency} topic for additional information about screening and laboratory testing for this condition.

Disease Overview

Incidence

- Carrier frequency: 1/120\textsuperscript{5}
- Variants confer\textsuperscript{5}
  - Profound BTD in 1/\sim 137,000
  - Partial BTD in 1/\sim 110,000
  - Profound and partial BTD (combined incidence) in 1/\sim 61,000

Symptoms

- Profound BTD (<10\% of normal biotinidase activity)\textsuperscript{3}
  - Seizures
  - Developmental delay
  - Hypotonia
  - Ataxia
  - Vision problems
  - Hearing loss
  - Alopecia
  - Rashes
- Partial BTD (10-30\% of normal biotinidase activity)\textsuperscript{3}
  - May manifest symptoms associated with profound BTD in times of stress (eg, surgery or infection)

Screening

- Newborn screening for BTD is performed across the United States (3-Strovel, 2017)
- Confirmatory testing following an abnormal newborn screen includes evaluation of enzyme activity in serum and may include molecular testing of the \textit{BTD} gene\textsuperscript{3}
Refer to the American College of Medical Genetics and Genomics Biotinidase Deficiency algorithm for more information.

Genetics

Gene

*BTD*

Inheritance

Autosomal recessive

Variants

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

Test Interpretation

Sensitivity/Specificity

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

Results

<table>
<thead>
<tr>
<th>Variant(s) Detected</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 pathogenic <em>BTD</em> gene variants identified on opposite chromosomes</td>
<td>Predicts a diagnosis of BTD</td>
</tr>
<tr>
<td>1 severe and 1 mild <em>BTD</em> gene variant identified</td>
<td>Predicts partial BTD</td>
</tr>
<tr>
<td>1 copy of a pathogenic <em>BTD</em> gene variant identified</td>
<td>Predicts that individual is at least a carrier of BTD</td>
</tr>
<tr>
<td>No pathogenic gene variants detected by sequencing</td>
<td>Likelihood is reduced that the individual is a carrier of or affected with BTD</td>
</tr>
</tbody>
</table>

*The variant database hosted by ARUP Laboratories is a helpful resource and 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 2020]


7. ARUP Laboratories, University of Utah Health. BTD Database. [Accessed: Feb 2020]