

BTD Gene Analysis in Biotinidase Deficiency

CLINICAL FEATURES

Biotinidase deficiency is a disorder of biotin metabolism. Patients are classified as having either a profound or partial deficiency based on measurement of biotinidase activity in serum. Clinical features of profound untreated biotinidase deficiency include seizures, ataxia, hypotonia, developmental delay, alopecia, hearing loss, eye problems, skin rash, lactic acidosis, ketosis, and spinal cord demyelination. Onset of symptoms usually occurs by several months of age but may occur during late childhood or adolescence. Partial biotinidase deficiency may exhibit any of the above symptoms but the symptoms are usually milder and may only occur during periods of metabolic stress. The symptoms of biotinidase deficiency can be prevented by administration of oral biotin making this disorder highly amenable to newborn screening programs in the U.S. and worldwide. However, once the eye, hearing problems, and developmental delay occur, they may be irreversible.^{1,6,7}

GENETICS

Biotinidase deficiency is caused by pathogenic variants in the *BTD* gene that encodes the enzyme biotinidase, which is responsible for recycling the biotin vitamin. Biotin is an important coenzyme for the proper function of four carboxylases involved in multiple metabolic pathways. The severity of the disease is related to the degree of enzyme deficiency with profound patients having less than 10% of mean normal activity and partial patients having between 10-30% mean normal activity. The *BTD* gene is located on chromosome 3p25 and has four exons. The incidence of biotinidase deficiency is approximately 1 in 80,000.^{1,2,3}

INHERITANCE PATTERN

Autosomal Recessive

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *BTD* gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

VARIANT SPECTRUM

BTD variants may occur throughout the gene and include missense, nonsense, splicing and small deletions/insertions, and large deletions.⁵ Almost all individuals with partial biotinidase deficiency have one D444H variant in combination with a variant for profound deficiency on the other allele.^{1,3,4} When D444H is in cis with the

A171T variant, the combination of both variants results in a severe allele which, when combined with a second severe allele in trans, will cause profound biotinidase deficiency.³ The genotype may predict the phenotype particularly when determining if an individual has a profound or partial deficiency; however, more detailed correlations are difficult due to the heterogeneity of symptoms even among members of the same family.¹

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