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 and ketosis. 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]

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:
Variant analysis of the *BTD* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *BTD* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

Test Sensitivity:

In patients with either profound or partial biotinidase deficiency, variant analysis identified a sequence variant in greater than 99% of alleles.[2,4,5] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

BTD variants may occur throughout the gene and include missense, nonsense, splicing and small deletions/insertions, and large deletions.[6] Almost all individuals with partial biotinidase deficiency have one D444H variant in combination with a variant for profound deficiency on the other allele.[1,3,5] 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]

References:

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4. Wolf et al. (2005) Human Mutation 25 (4):413 (PMID: 15776412)
5. Milánkovics et al. (2007) Molecular Genetics And Metabolism 90 (3):345-8 (PMID: 17185019)
6. Stenson et al. (2014) Human Genetics 133 (1):1-9 (PMID: 24077912)