Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	6/28/2021
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Biotinidase Deficiency (BTD) Sequencing

ARUP test code 3004424

Biotinidase Deficiency Specimen	Whole Blood
Biotinidase Deficiency Interp	Positive

RESULT
Two pathogenic variants were detected in the BTD gene.

PATHOGENIC VARIANT
Gene: BTD (NM_001370658.1)
Nucleic Acid Change: c.873del; Heterozygous
Amino Acid Alteration: p.Ser291ArgfsTer23
Also Known As: c.933delT; p.Ser311fs
Inheritance: Autosomal Recessive

PATHOGENIC VARIANT
Gene: BTD (NM_001370658.1)
Nucleic Acid Change: c.1270G>C; Heterozygous
Amino Acid Alteration: p.Asp424His
Also Known As: c.1330G>C; p.Asp444His
Inheritance: Autosomal Recessive

INTERPRETATION
Two pathogenic variants, c.873del; p.Ser291ArgfsTer23, and c.1270G>C; p.Asp424His were detected in the BTD gene by massively parallel sequencing. This result is consistent with a diagnosis of partial biotinidase deficiency if the variants are present on opposite chromosomes. Although the identified variants have not previously been reported to occur on the same chromosome, parental testing could confirm they are located on opposite chromosomes.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classifications:
The BTD c.873del; Ser291ArgfsTer23 variant (rs397514395; ClinVar Variation ID: 25052), also known as c.933delT; p.Ser311fs in traditional nomenclature, is reported in the literature in the compound heterozygous state in multiple individuals affected with profound or partial biotinidase deficiency (Borsatto 2014, Milankovics 2007, Pomponio 1997, Wolf 2002, Wolf 2017). This variant is found on only three chromosomes in the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. This variant causes a frameshift by deleting a single nucleotide in the last exon of the BTD gene. While this is not expected to lead to nonsense-mediated decay, this is predicted to result in a truncated protein lacking the last 233 amino acids of the BTD protein. Based on available information, this variant is considered to be pathogenic.

H=High, L=Low, *=Abnormal, C=Critical

The BTD c.1270G>C; p.Asp424His variant (rs13078881), also known as c.1330G>C; p.Asp444His for NM_000060.2, is reported in multiple patients with partial biotinidase deficiency (Dobrowolski 2003, Funghini 2002, Milankovics 2010, Muhl 2001, Pomponio 2000, Swango 1998, Wolf 2005), with a higher prevalence in affected individuals (Milankovics 2010). This variant is reported in ClinVar (Variation ID: 1900), and found in the general population with an overall allele frequency of 3.2% (9005/282830 alleles, including 199 homozygotes) in the Genome Aggregation Database. The aspartate at codon 424 is highly conserved, and computational analyses predict that the variant is deleterious (REVEL: 0.769). Based on available information, this variant is considered to be mildly pathogenic.

RECOMMENDATIONS
Genetic and metabolic consultations are indicated, including a discussion of medical screening and management. At-risk relatives should be offered testing for the identified variants (Familial Targeted Sequencing, ARUP test code 3005867). This individual's future reproductive partner should be offered carrier testing for biotinidase deficiency. Parental testing should be considered to confirm the chromosomal origin of the identified pathogenic variants.

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics.
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations: None

REFERENCES
Borsatto T et al. Biotinidase deficiency: clinical and genetic studies of 38 Brazilian patients. BMC Med Genet. 2014;15:96. PMID: 25174816.
Dobrowolski S et al. Real time PCR assays to detect common mutations in the biotinidase gene and application of mutational analysis to newborn screening for biotinidase deficiency. Mol Genet Metab. 2003 Feb;78(2):100-7. PMID: 12618081
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Milankovics I et al. Mutations causing biotinidase deficiency in children ascertained by newborn screening in Western Hungary. Mol Genet Metab. 2007;90(3):345-348. PMID: 17185019.
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Pomponio RJ et al. Mutations in the human biotinidase gene that cause profound biotinidase deficiency in symptomatic children: molecular, biochemical, and clinical analysis. Pediatr Res. 1997;42(6):840-848. PMID: 9396567
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Swango K et al. Partial biotinidase deficiency is usually due to the D444H mutation in the biotinidase gene. Hum Genet. 1998 May;102(5):571-5. PMID: 9654207.
Wolf B et al. Seventeen novel mutations that cause profound biotinidase deficiency. Mol Genet Metab. 2002;77(1-2):108-111. PMID: 12359137.
Wolf B et al. Biotinidase deficiency: novel mutations and their biochemical and clinical correlates. Hum Mutat. 2005 Apr;25(4):413. PMID: 9375914.
Wolf B. Successful outcomes of older adolescents and adults with profound biotinidase deficiency identified by newborn screening.

Genet Med. 2017;19(4):396-402. PMID: 27657684.

This result has been reviewed and approved by [redacted]

H=High, L=Low, *=Abnormal, C=Critical

BACKGROUND INFORMATION: Biotinidase Deficiency (BTD) Sequencing

CHARACTERISTICS: Deficiency in biotinidase enzymatic activity impairs the body's ability to recycle and reuse the vitamin biotin, resulting primarily in neurologic and dermatologic symptoms. Manifestations of profound biotinidase deficiency (BTD) include ataxia, hypotonia, developmental delay, seizures, vision problems, hearing loss, alopecia, metabolic ketolactic acidosis, organic aciduria, and hyperammonemia.

EPIDEMIOLOGY: The incidence of profound and partial biotinidase deficiency is approximately 1:60,000

CAUSE: Pathogenic germline variants in the BTD gene

INHERITANCE: Autosomal recessive

CLINICAL SENSITIVITY: 99 percent

GENE TESTED: BTD (NM_000060)* (NM_001370658)
* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of BTD. This test only detects variants within the coding regions and intron-exon boundaries of the BTD gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

SNVs and Indels will not be called in the following regions due to technical limitations of the assay:
BTD (NM_000060) exon(s) 1

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Biotinidase Deficiency Specimen	24-143-400490	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Biotinidase Deficiency Interp	24-143-400490	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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