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

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
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

INDICATION FOR TESTING
Confirm diagnosis

RESULT
Two pathogenic variants were detected in the BTD gene.

PATHOGENIC VARIANT
Gene: BTD (NM_001370658.1)
Nucleic Acid Change: c.38_44delinsTCC Heterozygous
Amino Acid Alteration: p.Cys13PhefsTer36
Also Known As: c.98_104delinsTCC; p.Cys33PhefsTer36
Inheritance: Autosomal recessive

PATHOGENIC VARIANT
Gene: BTD (NM_001370658.1)
Nucleic Acid Change: c.566G>A; Heterozygous
Amino Acid Alteration: p.Arg189His
Also Known As: c.626G>A; p.Arg209His
Inheritance: Autosomal recessive

INTERPRETATION
Two pathogenic variants, c.38_44delinsTCC; p.Cys13PhefsTer36 and c.566G>A; p.Arg189His, were detected in the BTD gene by massively parallel sequencing. This result is consistent with a diagnosis of profound biotinidase deficiency if the variants are located 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.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classifications: The BTD c.38_44delinsTCC; p.Cys13PhefsTer36 variant (rs80338684), also known as c.98_104delinsTCC; p.Cys33PhefsTer36 in transcript NM_000060.2, is reported in the literature in the homozygous or compound heterozygous state in multiple individuals affected with profound biotinidase deficiency (Pomponio, 1995; Senanayake, 2015; Ferreira, 2017; Al-Eitan, 2020; Wolf, 2000) and is also reported as pathogenic in ClinVar (Variation ID: 1895). This variant is observed on 36 alleles in the Genome Aggregation Database, with an allele frequency of 0.059% (18/30610 alleles)

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

in the South Asian population. This variant causes a frameshift by deleting seven and inserting three nucleotides, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

The BTD c.566G>A; p.Arg189His variant (rs398123139), also known as c.626G>A; p.Arg209His in transcript NM_000060.2, has been reported in an individual with profound biotinidase deficiency, and found in-trans with a pathogenic variant (Li, 2014). Another missense variant at this residue, p.Arg189Cys, has been reported in an individual with partial biotinidase deficiency when found with a pathogenic variant (Proctor, 2016). The p.Arg189His variant is listed as pathogenic or likely pathogenic in the ClinVar database (Variation ID: 92400) and is reported in the general population with an overall allele frequency of 0.0025% (7/282,856 alleles) in the Genome Aggregation Database. The arginine at residue 189 is moderately conserved and located in the carbon-nitrogen hydrolase domain. Based on the available information, the variant is classified as 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 pathogenic variants (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). This individual's 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 included in this report.

REFERENCES
Al-Eitan LN, et al. Identification and characterization of BTD gene mutations in Jordanian children with biotinidase deficiency. J Pers Med. 2020;10(1):4. PMID: 31973013.

Ferreira P, et al. Irreversibility of symptoms with biotin therapy in an adult with profound biotinidase deficiency. JIMD Rep. 2017;36:117-120. PMID: 28220409.

Li H, et al. Novel mutations causing biotinidase deficiency in individuals identified by newborn screening in Michigan including an unique intronic mutation that alters mRNA expression of the biotinidase gene. Mol Genet Metab. 2014;112(3):242-6. PMID: 24797656.

Pomponio RJ, et al. Mutational hotspot in the human biotinidase gene causes profound biotinidase deficiency. Nat Genet. 1995;11(1):96-8. PMID: 7550325.

Procter M, et al. Forty-eight novel mutations causing biotinidase deficiency. Mol Genet Metab. 2016;117(3):369-72. PMID: 26810761.

Senanayake DN, et al. First contiguous gene deletion causing biotinidase deficiency: the enzyme deficiency in three Sri Lankan children. Mol Genet Metab Rep. 2015;2:81-84. PMID: 28649532.

Wolf B, et al. Biotinidase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. University of Washington, Seattle; 1993-2021. Mar 2000 (updated Jun 2016). PMID: 20301497. https://www.ncbi.nlm.nih.gov/books/NBK1322/

This result has been reviewed and approved by [redacted]

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BACKGROUND INFORMATION: Biotinidase Deficiency (BTD) Sequencing

CHARACTERISTICS: Deficiency in biotinidase enzymatic activity impairs the bodys 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	22-054-112641	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Biotinidase Deficiency Interp	22-054-112641	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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