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

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/14/2013
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Exome Reanalysis (Originally Tested at ARUP - No Specimen Required)

ARUP test code 3001457

Exome Reanalysis Interpretation

Positive

TEST PERFORMED
Exome reanalysis was performed using the original exome sequencing data from report date 1/20/2017, the current bioinformatics pipeline, updated population frequency data, and any new information provided about the patient's clinical findings. The overall result remains unchanged.

Result
Primary findings: Positive; one de novo pathogenic variant was detected in the ARID1B gene
Secondary findings: Negative

KEY CLINICAL FINDINGS
Hypercalcemia, hyperparathyroidism, hyperkalemia, hypotonia, short stature, nystagmus, and a history of non-regressive global developmental delay. He has distinctive facial features including narrow bifrontal diameter, long/narrow face, full vermillion of the lips, low nasal root. He was a full term infant with a two-vessel cord and has a history of bilateral cryptorchidism, pelviectasis, arachnoid cyst, C1 hypoplasia and dysphagia with aspiration.

HPO terms used: HP:0000256 (Macrocephaly), HP:0000275 (Narrow face), HP:0000639 (Nystagmus), HP:0000843 (Hyperparathyroidism), HP:0000952 (Jaundice), HP:0001252 (Hypotonia), HP:0001263 (Global developmental delay), HP:0002015 (Dysphagia), HP:0002153 (Hyperkalemia), HP:0100702 (Arachnoid cyst), HP:0003072 (Hypercalcemia), HP:0004322 (Short stature), HP:0005280 (Depressed nasal bridge), HP:0008434 (Hypoplastic cervical vertebrae), HP:0008689 (Bilateral cryptorchidism), HP:0010945 (Fetal pyelectasis)

INTERPRETATION
One de novo pathogenic variant was identified in the ARID1B gene. Pathogenic germline variants in ARID1B are associated with autosomal dominant Coffin-Siris syndrome 1 (MIM: 135900). An additional variant that may also be related to the patient's phenotype is listed below.

ARID1B gene, de novo pathogenic variant, autosomal dominant inheritance pattern
TNFSF10 gene, de novo variant of uncertain significance, unknown inheritance pattern

DE NOVO PATHOGENIC VARIANT
Gene: ARID1B (NM_001374820.1)
OMIM disease: Coffin-Siris syndrome 1 (MIM: 135900)
Inheritance pattern: Autosomal dominant
Variant: c.5274G>A; p.Gln1758= - Heterozygous
Chr6(GRCh37):g.157525130

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

Frequency: not in gnomAD
Computational prediction programs: Predicted to weaken canonical splice donor site

Common clinical features of Coffin-Siris syndrome may include developmental delay/intellectual disability, hypotonia, distinctive facial features, hypertrichosis, sparse scalp hair, and hypoplastic or absent fifth fingernails or toenails (van der Sluijs 2019). Other features may include slow growth, feeding difficulties, recurrent infections, ophthalmologic issues, hearing impairment, and congenital anomalies affecting the cardiac, gastrointestinal, genitourinary, or central nervous systems. Endocrinological abnormalities including hypothyroidism are reported, although hyperparathyroidism has not been specifically described, to our knowledge. The detected c.5274G>A; p.Gln1758= variant, also known as c.5025G>A; p.Gln1675= in transcript NM_020732.3, is reported de novo in an individual affected with Coffin-Siris syndrome (van der Sluijs 2019). Research studies on RNA from the current patient indicate the variant leads to skipping of exon 18, which is predicted to lead to a frameshift. Based on available information, this variant is considered to be pathogenic.

DE NOVO VARIANT OF UNCERTAIN SIGNIFICANCE
The following is a rare de novo variant in a gene with unknown significance/inheritance pattern:

Gene: TNFSF10 (NM_003810.4)
Variant: c.133-1G>A - Heterozygous
Chr3(GRCh37):g.172232789
Frequency: not in gnomAD
Computational prediction programs: Predicted to abolish canonical splice acceptor site

Close attention has been paid to the following genes associated with hyperparathyroidism and hypercalcemia: AIRE, ALPL, AP2S1, CASR, CDC73, CDKN1A, CDKN1B, CDKN1C, CDKN2B, CDKN2C, CYP24A1, GCM2, GNA11, MEN1, PTH, PTH1R, RET, TRPV6. No rare variants considered likely to affect protein function were detected.

No secondary pathogenic variants were detected in the v3.1 list of genes that the American College of Medical Genetics and Genomics (ACMG) recommends reporting in all individuals undergoing exome sequencing (Miller 2022). A list of ACMG genes is included in the additional technical information. These genes are evaluated only to the extent that standard exome sequencing allows. Single pathogenic variants in autosomal recessive ACMG genes are not reported.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Although the identified ARID1B variant is presumed to be de novo and recurrence risk is thought to be low, this patient's parents should be offered the option of prenatal diagnosis for the identified variant in future pregnancies. Future offspring of this individual have a 50 percent chance of inheriting the causative variant; thus, this patient should also be offered prenatal diagnostic options when of reproductive age.

NOTES
Deep intronic variants, variants in the untranslated regions and large deletions/duplications are not analyzed by this method; therefore, additional variants in the reported genes have not been excluded.
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics.

REFERENCES
Miller DT et al. ACMG SF v3.1 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and

Genomics (ACMG). Genet Med. 2022 Jul;24(7):1407-1414. PMID: 35802134.

van der Sluijs PJ et al. The ARID1B spectrum in 143 patients: from nonsyndromic intellectual disability to Coffin-Siris syndrome. Genet Med. 2019 Jun;21(6):1295-1307. PMID: 30349098.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Exome Reanalysis (Originally Tested at ARUP - No Specimen Required)

CHARACTERISTICS: Exome reanalysis may be performed when a previous exome analysis fails to determine the etiology for a suspected genetic condition. Rapid progress in the understanding of gene-disease relationships, in addition to improvements in variant-calling pipelines, underscores the utility of performing a bioinformatic-restricted reanalysis.

CLINICAL SENSITIVITY: Approximately 10-28 percent of non-diagnostic clinical exomes receive a definitive diagnosis upon reanalysis.

METHODOLOGY: A FastQ file of massively parallel sequencing (MPS) data from the original exome test was processed through our current variant calling and annotation pipeline. If the original sample(s) was available, Sanger sequencing was performed as necessary to confirm reported variants. Human genome build 19 (Hg19) was used for data analysis.

LIMITATIONS OF ANALYSIS: The human exome cannot be completely analyzed as some genes have not been identified while others, due to technical limitations, cannot either be sequenced or interpreted. Some pathogenic variants reside in regions outside the exome. This test only detects variants within the coding regions and intron-exon boundaries of genes targeted in the original capture. Regulatory region variants and deep intronic variants will not be identified. Mitochondrial DNA is not analyzed. Chromosomal phase of identified variants may not be determined. Deletions/duplications/insertions of any size may not be detected by MPS. Diagnostic errors can occur due to rare sequence variations. Variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level somatic variants associated with disease. Please see Additional Technical Information located at http://ltd.aruplab.com/Tests/Pub/2006332 for more information. A negative result does not exclude a genetic diagnosis.

LIMITATIONS FOR REPORTING AND INTERPRETATION: Only variants in genes suspected to be associated with the patient's symptoms are reported, with the exception of secondary pathogenic findings, if elected. Additionally, de novo and/or rare compound heterozygous variants in genes of unknown clinical relevance maybe reported. Incorrect reporting of biological relationships among family members may affect result interpretation. Mode of inheritance, reduced penetrance, and genetic heterogeneity could reduce clinical sensitivity. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Exome Reanalysis Interpretation	22-241-401732	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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