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

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
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 10/03/2015, the current bioinformatics pipeline, updated population frequency data, and any new information provided about the patient's clinical findings. The overall result has changed from uncertain to positive based on a causative variant identified in the SMARCB1 gene.

RESULT
Primary findings: Positive; one de novo pathogenic variant was detected in the SMARCB1 gene
Secondary findings: Negative

KEY CLINICAL FINDINGS
Developmental delay, intellectual disability, coarse facial features, feeding difficulties, hypoplastic fifth fingernails.

HPO terms used: HP:0001263 (Global developmental delay), HP:0001249 (Intellectual disability), HP:0000280 (Coarse facial features), HP:0011968 (Feeding difficulties), HP:0008398 (Hypoplastic fifth fingernail).

INTERPRETATION
One de novo pathogenic variant was identified in the SMARCB1 gene. Pathogenic germline SMARCB1 variants are associated with autosomal dominant Coffin-Siris syndrome 3 (MIM: 614608; OMIM(R)). Additional variants that may also be related to the patient's phenotype are listed below.

SMARCB1 gene, de novo heterozygous pathogenic variant, autosomal dominant inheritance
SPRY4 gene, de novo heterozygous variant of uncertain significance, autosomal dominant inheritance
NTF4 gene, de novo heterozygous variant of uncertain significance, unknown inheritance pattern

DE NOVO PATHOGENIC VARIANT
Gene: SMARCB1 (NM_003073.4)
OMIM(R) disease: Coffin-Siris syndrome 3 (MIM: 614608)
Inheritance pattern: Autosomal dominant
Variant: c.1121G>A; p.Arg374Gln - Heterozygous
Chr22(GRCh37):g.24176330
Frequency: gnomAD: 1 out of 206,508 chromosomes (low confidence), overall MAF 0.00048%
Computational prediction programs: Deleterious (REVEL: 0.930)

Pathogenic germline variants in SMARCB1 have been associated with Coffin-Siris syndrome 3 (MIM: 614608) and may confer susceptibility to schwannomatosis-1 (MIM: 162091) and Rhabdoid

tumor predisposition syndrome 1 (MIM: 609322; OMIM(R)). The identified c.1121G>A; p.Arg374Gln variant (ClinVar Variation ID: 372511) has been reported in the medical literature in two individuals who were diagnosed with Coffin-Siris syndrome, including one de novo occurrence (Gossai, 2015; Wieczorek, 2015). Based on the available evidence, the c.1121G>A; p.Arg374Gln variant is classified as pathogenic.

DE NOVO VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: SPRY4 (NM_030964.3)
OMIM(R) disease: Hypogonadotropic hypogonadism 17 with or without anosmia (MIM: 615266)
Inheritance pattern: Autosomal dominant
Variant: c.769C>T; p.Arg257Cys - Heterozygous
Chr5(GRCh37):g.141693974
Frequency: gnomAD: 2 out of 249,922 chromosomes, overall MAF 0.00080%
Computational prediction programs: Deleterious (REVEL: 0.0.806)

The SPRY4 c.769C>T; p.Arg257Cys variant, to our knowledge, is not reported in the medical literature or gene specific databases. Based on the available information, the clinical significance of this variant is uncertain.

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

Gene: NTF4 (NM_006179.4)
Variant: c.271C>T; p.Arg91Trp - Heterozygous
Chr19(GRCh37):g.49564984
Frequency: gnomAD: 1 out of 243688 chromosomes, overall MAF 0.00041%
Computational prediction programs: Uncertain (REVEL: 0.685)

No secondary pathogenic variants were detected in the v3.2 list of genes that the American College of Medical Genetics and Genomics (ACMG) recommends reporting in all individuals undergoing exome sequencing (Miller, 2023). 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 SMARCB1 variant is presumed to be de novo and recurrence risk is thought to be low, the patient's parents should be offered the option of prenatal diagnosis for the identified variant in future pregnancies. The patient's parents should be offered the options of preimplantation genetic diagnosis and/or prenatal diagnosis with future pregnancies.

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
Gossai N, et al. Report of a patient with a constitutional missense mutation in SMARCB1, Coffin-Siris phenotype, and schwannomatosis. Am J Med Genet A. 2015 Dec;167A(12):3186-91. PMID: 26364901.
Miller DT, et al. ACMG SF v3.2 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. 2023 Jun 15:100866. PMID: 37347242.

Wieczorek D, et al. A comprehensive molecular study on Coffin-Siris and Nicolaides-Baraitser syndromes identifies a broad molecular and clinical spectrum converging on altered chromatin remodeling. Hum Mol Genet. 2013 Dec 20;22(25):5121-35. PMID: 23906836.

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/

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Exome Reanalysis Interpretation	24-352-103090	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