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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

Section 79-1 of New York State Civil Rights Law requires informed consent be obtained from patients (or their legal guardians) prior to pursuing genetic testing. These forms must be kept on file by the ordering physician. Consent forms for genetic testing are available at www.aruplab.com. Incidental findings are not reported unless clinically significant but are available upon request.

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

Exome reanalysis was performed using the original exome sequencing data from 05/03/2013, the current bioinformatics pipeline, updated population frequency data, and any new information provided about the patients clinical symptoms. The overall result has changed to positive based on a causative variant identified in the SMARCB1 gene.

RESULT
Positive; one pathogenic variant was identified in the SMARCB1 gene that is predicted to provide an explanation for this individuals phenotype.

INDICATION FOR TESTING
[Patient medical history and indication for testing]

INTERPRETATION
One de novo pathogenic variant was identified in the SMARCB1 gene. Pathogenic SMARCB1 variants are associated with autosomal dominant Coffin-Siris syndrome 3. Other variants that may be related to this patients symptoms are listed below.

SMARCB1 gene, de novo pathogenic variant, autosomal dominant inheritance

SPRY4 gene, de novo variant of uncertain significance, autosomal dominant inheritance

NTF4 gene, de novo variant of uncertain significance, unknown inheritance pattern

SIPA1L3 gene, de novo variant of uncertain significance, autosomal recessive inheritance

DE NOVO PATHOGENIC VARIANT
Gene: SMARCB1 (NM_003073.4)
Variant: c.1121G>A; p.Arg374Gln - Heterozygous
Chr22(GRCh37):g.24176330

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

Frequency: rs1057517825; gnomAD: 1 out of 206,508 chromosomes (low confidence), overall MAF 0.00048%
Conservation: Highly conserved amino acid (Alamut software v2.11.0)
Computational prediction programs: Deleterious (SIFT: damaging, PolyPhen2: possibly damaging)
Inheritance pattern: Autosomal dominant

One pathogenic variant, c.1121G>A; p.Arg374Gln, was identified in the SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 E (SMARCB1) gene by massively parallel sequencing and confirmed by Sanger sequencing. This variant was not detected in either of the patients parents as confirmed by targeted Sanger sequencing. Thus, it is likely de novo, though the possibility of parental germline mosaicism cannot be excluded. 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).

The identified c.1121G>A; p.Arg374Gln variant has been reported in the medical literature in two individuals who were diagnosed with Coffin-Siris syndrome. It was confirmed to be de novo in one of these individuals whose features included intellectual disability, coarse facies, low frontal hairline, scoliosis, cryptorchidism, and congenital heart defects (Wieczorek 2015). The inheritance was not determined for the other individual who presented early in life with moderate intellectual disability, hypotonia, mild microcephaly, coarse facies, wide mouth with full lips, hypoplasia of the digits, and general hirsutism and who developed schwannomatosis in adulthood (Gossai 2015). This variant is reported as pathogenic in ClinVar (Variation ID: 372511). 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)
Variant: c.769C>T; p.Arg257Cys - Heterozygous
Chr5(GRCh37):g.141693974
Frequency: rs911410685; gnomAD: 2 out of 249,922 chromosomes, overall MAF 0.00080%
Conservation: Highly conserved amino acid (Alamut software v2.11.0)
Computational prediction programs: Deleterious (REVEL: 0.806)
Inheritance pattern: Autosomal dominant

One variant of uncertain significance, c.769C>T; p.Arg257Cys, was identified in the sprouty RTK signaling antagonist 4 (SPRY4) gene by massively parallel sequencing and confirmed by Sanger sequencing. This variant was not detected in either of the patients parents as confirmed by targeted Sanger sequencing. Thus, it is likely de novo, but the possibility of parental germline mosaicism cannot be excluded. The SPRY4 gene encodes protein sprouty homolog 4 and has been associated with hypogonadotropic hypogonadism-17 with or without anosmia (MIM: 615266).

The identified 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.

DE NOVO VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: NTF4 (NM_006179.4)
Variant: c.271C>T; p.Arg91Trp - Heterozygous
Chr19(GRCh37):g.49564984
Frequency: rs1015733961; gnomAD: 1 out of 243688 chromosomes, overall MAF 0.00041%
Conservation: Highly conserved amino acid (Alamut software v2.11.0)
Computational prediction programs: Uncertain (REVEL: 0.685)

Inheritance pattern: Unknown

One variant of uncertain significance, c.271C>T; p.Arg91Trp, was identified in the neurotrophin 4 (NTF4) gene by massively parallel sequencing and confirmed by Sanger sequencing. This variant was not detected in either of the patients parents as confirmed by targeted Sanger sequencing. Thus, it is likely de novo, but the possibility of parental germline mosaicism cannot be excluded. The NTF4 gene has been associated with primary open angle glaucoma-1O (MIM: 613100).

The identified c.271C>T; p.Arg91Trp 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.

DE NOVO VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: SIPA1L3 (NM_015073.2)
Variant: c.3832G>A; p.Ala1278Thr - Heterozygous
Chr19(GRCh37):g.38655170
Frequency: rs762325718; gnomAD: 4 out of 251,048 chromosomes, overall MAF 0.0016%
Conservation: Highly conserved amino acid (Alamut software v2.11.0), but zebra finch has threonine at this position
Computational prediction programs: Neutral (REVEL: 0.144)
Inheritance pattern: Autosomal recessive

One variant of uncertain significance, c.3832G>A; p.Ala1278Thr, was identified in the signal induced proliferation associated 1 like 3 (SIPA1L3) gene by massively parallel sequencing and confirmed by Sanger sequencing. This variant was not detected in either of the patients parents as confirmed by targeted Sanger sequencing. Thus, it is likely de novo, but the possibility of parental germline mosaicism cannot be excluded. The SIPA1L3 gene has been associated with congenital cataract-45 (MIM: 616851).

The identified c.3832G>A; p.Ala1278Thr 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. No other rare variants were detected in SIPA1L3. While this reduces the likelihood of a second variant, deep intronic variants, variants in the untranslated region and large deletions are not analyzed by this method; therefore, a second variant in SIPA1L3 cannot be excluded.

Close attention has been paid to the following genes associated with Bartter syndrome and Gitelman syndrome: CLCNKA, CLCNKB, BSND, KCNJ1, SLC12A1, MAGED2, and SLC12A3. However, no rare variants considered likely to affect protein function were detected. Please note that variants in the following exons have not been excluded due to insufficient coverage: CLCNKA (NM_004070.3) exon 9, CLCNKB (NM_000085.4) exon 9, and MAGED2 (NM_177433.2) exon 9.

No pathogenic variants were identified in genes that were reviewed related to the following HPO terms: developmental regression (HP:0002376), cerebellar hemispheric hypogenesis (HP:0007360), nephrocalcinosis (HP:0000121), failure to thrive (HP:0001508), and polyhydramnios (HP:0001561). Please note that adequate sequencing coverage has not been verified for all HPO-related genes.

No secondary pathogenic variants were detected in the list of genes that the American College of Medical Genetics and Genomics (ACMG) recommends reporting in all individuals undergoing exome sequencing; note that single pathogenic variants in recessive ACMG genes are not reported. A list of currently recommended ACMG genes is included in the background information included in this report. These genes are evaluated only to the extent that standard exome sequencing allows.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Surveillance of the medical literature for new information regarding the identified variant and gene is recommended. Although the identified SMARCB1 variant is presumed to be de novo and recurrence risk is thought to be low, the patients parents should be offered the option of prenatal diagnosis for the identified variant in future pregnancies (Familial Mutation, Targeted Sequencing, Fetal; ARUP test code 2001980).

NOTES
None

REFERENCES
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This result has been reviewed and approved by Pinar Bayrak-Toydemir, M.D., Ph.D.

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

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 | 19-123-124284 | 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