ARUP LABORATORIES
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Jonathan R. Genzen, MD, PhD, Chief Medical Officer

Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: TEST,

Patient: POS EXAMPLE, RWGS REA

DOB

Sex: Female

Patient Identifiers: 49770

Visit Number (FIN): 50125

Collection Date: 6/12/2023 07:40

Whole Genome Reanalysis

ARUP test code 3005939

RWGS REA Int

Positive

TEST PERFORMED
Genome reanalysis was performed using the original rapid whole genome sequencing data from report date 05/15/2022, 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 negative to positive based on a causative variant identified in the SMARCB1 gene.

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

KEY CLINICAL FINDINGS
Failure to thrive, developmental regression, polyhydramnios, dysmorphic features that include cleft palate, posteriorly rotated left ear, broad nasal root, and abnormal frontal hairline.

HPO terms used:
HP:0002376 (Developmental regression), HP:0007360 (cerebellar hemispheric hypogenesis), HP:0000121 (nephrocalcinosis), HP:0001508 (failure to thrive), and HP:0001561 (polyhydramnios).

INTERPRETATION
One de novo pathogenic variant was identified in the SMARCB1 gene. Pathogenic SMARCB1 variants are associated with autosomal dominant Coffin-Siris syndrome 3.

DE NOVO PATHOGENIC VARIANT
Gene: SMARCB1 (NM_003073.4)
OMIM disease: Coffin-Siris syndrome 3 (MIM: 614608)
Inheritance pattern: Autosomal dominant
Variant: c.1121G>A; p.Arg374Gln - heterozygous
Chr22(GRCh37):g.24176330
Frequency: Not in gnomAD

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 SMARCB1 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).

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

Unless otherwise indicated, testing performed at:

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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.

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 genome 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 genome 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 (Familial Targeted Sequencing, Fetal, ARUP test 3005869).

NOTES
Intergenic variants, deep intronic variants not predicted to alter splicing, large deletions/duplications, and chromosomal rearrangements are not analyzed by this method; therefore, additional variants in the reported genes have not been excluded. Refer to background for details of limitations. 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;167A(12):3186-3191. PMID: 26364901.

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;24(7):1407-1414. PMID: 35802134.

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;22(25):5121-5135. PMID: 23906836.

BACKGROUND INFORMATION: Whole Genome Reanalysis (Originally Tested at ARUP - No Specimen Required)
CHARACTERISTICS: Genome reanalysis may be performed when a previous genome 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: Varies based on clinical symptoms, family history, inheritance pattern, and previous clinical evaluations

METHODOLOGY: A FastQ file of massively parallel sequencing (MPS) data from the original genome 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: A negative result does not exclude a genetic diagnosis. The human genome cannot be completely analyzed as some genes have not been identified while others, due to technical limitations, cannot be sequenced or interpreted. Variants in intergenic or deep intronic regions will only be evaluated if an effect on gene expression is predicted via annotation software. 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 is not designed to detect low-level somatic variants associated with disease. Please see Additional Technical Information located at http://ltd.aruplab.com/Tests/Pub/3005939 for more information.

LIMITATIONS FOR REPORTING AND INTERPRETATION: Only variants in genes suspected to be causative of the patient's symptoms are reported, with the exception of secondary pathogenic findings, if elected. 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.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. 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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
RWGS REA Int	23-163-100684	6/12/2023 7:40:00 AM	6/12/2023 7:41:03 AM	6/12/2023 7:42:00 AM

END OF CHART

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