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

Physician: Doctor, Example

Patient: Patient, Example

DOB	9/28/2015
Gender:	Female
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

See Note

TEST PERFORMED
Exome reanalysis was performed using the original exome sequencing data from report date 10/23/2021, the current bioinformatics pipeline, updated population frequency data, and any new information provided about the patient's clinical findings. The overall result remains unchanged. Variants from the original exome report that are now believed unlikely related to the patient's phenotype have been moved to the end of the report.

RESULT
Primary findings: Negative
Secondary findings: Negative

KEY CLINICAL FINDINGS
According to information provided to ARUP Laboratories, the patient is an 8-year-old female of Ashkenazi Jewish, European, Native American, and Japanese descent with global developmental delay, pes planus, tibial tendon dysfunction, allergic rhinitis, astigmatism, and hypotonia. She was delivered vaginally at 38 weeks gestation and noted to have congenital hypotonia; her weight, length and head circumference were in the normal range. She has had osteotomy calcaneus to lengthen her Achilles tendons bilaterally. Since the time of her initial exome sequencing, she is also noted to have generalized epilepsy, abnormal behaviors, and suspected autism spectrum disorder. Previous testing has included plasma amino acids, acylcarnitine profile, urine organic acids, total and free carnitine, CK, lactic acid, pyruvic acid, CMP, triglycerides, and uric acid studies. A neuromuscular panel previously demonstrated variants of unknown significance in LAMB2 c.3157_5159del (paternally inherited) as well as COL6A1 c.2642C>T and SYNE1 c.22700G>A (both maternally inherited). Brain MRI at age 5 and pelvic X-rays were normal. Exome sequencing performed previously at ARUP (accession no: 21-246-402155) was negative. A cytogenomic SNP microarray (ARUP accession no: 24-257-144083) was also normal. Her mother and maternal grandmother are affected with a similar condition including global delay and muscle weakness.

HPO terms used:
HP:0002197 (Generalized-onset seizure), HP:0000717 (Autism), HP:0000708 (Atypical behavior), HP:0001319 (Neonatal hypotonia), HP:0001263 (Global developmental delay), HP:0001252 (Hypotonia), HP:0001763 (Pes planus), HP:0001382 (Joint hypermobility)

INTERPRETATION
A unifying cause for the patient's condition could not be identified. Variants of uncertain clinical significance identified by previous genetic testing and also identified in this sample are listed below.

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

Gene: LAMB2 (NM_002292.4; MIM: 150325)
Variant c.3157_3159delCCT; p.Pro1053del - Heterozygous

Gene: SYNE1 (NM_033071.4: MIM: 608441)
Variant: c.22700G>A; p.Gly7567Asp - Heterozygous

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.

LIKELY BENIGN VARIANT
Gene: COL6A1 (NM_001848.3; MIM: 120220, OMIM(R))
Variant: c.2642C>T; p.Thr881Met - Heterozygous
Chr21(GRCh37):g. 47423482
Frequency: 185 out of 276910 chromosomes, overall MAF 0.067%, Genome Aggregation Database (v2.1.1)
Computational prediction programs: Uncertain (REVEL: 0.177)

Due to new information regarding the frequency of this variant in the general population, this variant has been reclassified from a variant of uncertain significance to likely benign.

RECOMMENDATIONS
Medical management and screening should rely on clinical findings. Genetic consultation and surveillance of the medical literature for new information regarding the identified variants and genes are recommended.

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.

Adequate sequencing coverage has not been verified for each of the genes reported. If the autosomal recessive disease fits well with the clinical findings, consideration for full gene targeted analysis of the gene of interest should be given.

Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics.

REFERENCES
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.

This result has been reviewed and approved by [redacted]

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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	24-270-401720	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