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

Physician: TEST,

Patient: UNCERTAIN, EXOME PRO

DOB
Sex: Female
Patient Identifiers: 51718
Visit Number (FIN): 52105
Collection Date: 8/21/2023 07:38

Exome Sequencing

ARUP test code 3016583

EXOME PRO Int

Uncertain

TEST PERFORMED
Exome Sequencing
Samples tested: Proband and both parents

RESULT
Primary findings: Uncertain
Secondary findings: Negative

KEY CLINICAL FINDINGS
Generalized-onset seizure, global developmental delay, limb fasciculations, microcephaly, and tremor.

HPO terms used: HP:0002197 (generalized-onset seizure), HP:0001263 (global developmental delay) HP:0007289 (limb fasciculations), HP:0000252 (microcephaly), HP:0001337 (tremor).

INTERPRETATION
A unifying cause for the patient's condition could not be identified. Variants that may be related to the reported phenotype are listed below. No rare coding de novo variants (population frequency of less than one percent) were identified.

TUBGCP2 gene, compound heterozygous variants of uncertain significance, autosomal recessive inheritance
RYR3 gene, paternally inherited variant of uncertain significance, unknown inheritance pattern
FASN gene, paternally inherited variant of uncertain significance, unknown inheritance pattern
GLDC gene, maternally inherited variant of uncertain significance, autosomal recessive inheritance

COMPOUND HETEROZYGOUS VARIANTS OF UNCERTAIN SIGNIFICANCE
Gene: TUBGCP2 (NM_006659.3)
OMIM disease: Pachygyria, microcephaly, developmental delay, and dysmorphic facies, with
or without seizures (MIM: 618737)
Inheritance pattern: Autosomal recessive
Paternally Inherited Variant: c.889C>T; p.Arg297Cys, heterozygous
Chr10(GRCh37):g.135106678
Frequency: gnomAD: 27 out of 282350 chromosomes, overall MAF 0.0096%
Computational prediction programs: Uncertain (REVEL: 0.386)

Maternally Inherited Variant: c.964C>T; p.Gln322Ter, heterozygous
Chr10(GRCh37):g.135106603
Frequency: gnomAD: 1 out of 250938 chromosomes, overall MAF 0.0004%

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

The TUBGCP2 gene has been associated with autosomal recessive pachygyria, microcephaly, developmental delay, and dysmorphic facies, with or without seizures. In at least one individual, developmental regression was noted with the onset of seizures (Mitani, 2019).

The TUBGCP2 c.889C>T; p.Arg297Cys variant is reported in the literature in an individual with delayed motor and language development, microcephaly, mild myopia and astigmatism, smooth philtrum and prominent ears but otherwise nondysmorphic. This individual also displayed pachygyria in temporal and posterior lobes and bilateral T2-hyperintense abnormalities of the white matter and thin corpus callosum (Mitani, 2019). This individual carried a loss of function TUBGCP2 splice variant on the opposite allele. Due to limited information, the clinical significance of the p.Arg297Cys variant is uncertain at this time.

The TUBGCP2 c.964C>T; p.Gln322Ter variant, to our knowledge, is not reported in the medical literature or gene specific databases. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Due to limited information, the clinical significance of this variant is uncertain at this time.

VARIANT OF UNCERTAIN SIGNIFICANCE IN AUTOSOMAL RECESSIVE GENE
The following is a rare heterozygous variant of uncertain significance in a gene with an autosomal recessive inheritance pattern and associated with a phenotype that corresponds with this individual's clinical findings.

Gene: GLDC (NM_000170.3)
OMIM disease: Glycine encephalopathy (MIM: 605899)
Maternally Inherited Variant: c.835C>A; p.Leu279Ile, heterozygous
Chr9(GRCh37):g.6605157
Frequency: gnomAD: 3 out of 282856 chromosomes, overall MAF 0.001%
Computational prediction programs: Uncertain (REVEL: 0.529)

RARE VARIANTS OF UNCERTAIN SIGNIFICANCE
The following are rare de novo variants in genes with unknown significance/inheritance pattern:

Gene: RYR3 (NM_001036.4)
Paternally Inherited Variant: c.5861-3C>T, heterozygous
Chr15(GRCh37):g.33988416
Frequency: gnomAD: 8 out of 247122 chromosomes, overall MAF 0.003%
Computational prediction programs: Not predicted to significantly impact splicing (Alamut software v2.11.0)

Gene: FASN (NM_004104.5)
Paternally Inherited Variant: c.6910G>A; p.Val2304Met, heterozygous
Chr17(GRCh37):g.80038383
Frequency: gnomAD: 8 out of 202478 chromosomes, overall MAF 0.004%
Computational prediction programs: Neutral (REVEL: 0.091)

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
Medical management and screening should rely on clinical

findings. Due to the documented association of various eye anomalies with TUBGCP2 variants in the literature, consideration should be given to ophthalmological exam for this individual. Genetic consultation and surveillance of the medical literature for new information regarding the identified variants and genes are recommended.

NOTES
Approximately 95.1% of bases in the coding exome were covered by more than 10 sequencing reads.
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.

Mitani T, et al. Bi-allelic pathogenic variants in TUBGCP2 cause microcephaly and lissencephaly spectrum disorders. Am J Hum Genet. 2019;105(5):1005-1015. PMID: 31630790.

This result has been reviewed and approved by

BACKGROUND INFORMATION: Exome Sequencing

CHARACTERISTICS: The purpose of exome sequencing is to determine the patient's diagnosis when a Mendelian genetic condition is suspected. The exome includes all known nuclear genes and accounts for approximately 1-2 percent of the human genome. However, it is estimated that the exome harbors approximately 85 percent of genetic disease-causing variants.

CLINICAL SENSITIVITY: Varies based on clinical testing indication, previous clinical evaluations, and availability of parental control samples. A diagnosis is determined in 30-35 percent of patients when parental samples are submitted as exome sequencing controls. Diagnostic rates decrease to approximately 20 percent when parental samples are unavailable.

CLINICAL SENITIVITY: Varies based on clinical testing indication, previous clinical evaluations, and availability of parental control samples. A diagnosis is determined in approximately 20-40% of individuals; higher diagnostic rates are reported when parental samples are submitted as exome sequencing controls. Mode of inheritance, reduced penetrance, and genetic heterogeneity can reduce clinical sensitivity.

METHODOLOGY: Targeted capture of all (or selected) coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 98 percent for single nucleotide variants (SNVs) and greater than 93 percent for Insertions / duplications / deletions from 1-10 base pairs in size. Deletions/duplication greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS OF ANALYSIS: A negative result does not exclude all genetic diagnoses. The human exome is not able to 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 the targeted genes. Regulatory region variants, deep intronic variants, and large deletions/duplications 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 massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, 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.

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 may be reported. Incorrect reporting of biological relationships among family members may affect result interpretation. 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
EXOME PRO Int	23-233-100746	8/21/2023 7:38:00 AM	8/21/2023 7:39:52 AM	8/21/2023 7:42:00 AM

END OF CHART

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