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

Long QT Panel, Sequencing and Deletion/Duplication

ARUP test code 3001603

Long QT Specimen: Whole Blood

Long QT Interp: Positive

RESULT
One pathogenic variant was detected in the KCNQ1 gene.

PATHOGENIC VARIANT
Gene: KCNQ1 (NM_000218.2)
Nucleic Acid Change: c.830C>T; Heterozygous
Amino Acid Alteration: p.Ser277Leu
Inheritance: Autosomal dominant, autosomal recessive

INTERPRETATION
One pathogenic variant, c.830C>T; p.Ser277Leu, was detected in the KCNQ1 gene by massively parallel sequencing. Pathogenic variants in KCNQ1 are associated with autosomal dominant familial atrial fibrillation 3 (MIM: 607554), long QT syndrome 1 (MIM: 192500), and short QT syndrome 2 (MIM: 609621), and autosomal recessive Jervell and Lange-Nielsen syndrome (MIM: 220400). This result is consistent with a diagnosis of a KCNQ1-related disorder. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology and limitations of this test.

Evidence for variant classification:
The KCNQ1 c.830C>T; p.Ser277Leu variant (rs199472730) is reported in the literature in numerous individuals affected with long QT syndrome and has been observed to segregate with disease in multiple families (Aidery 2011, Chen 2011, Liu 2002, Yagi 2018). This variant is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. The serine at codon 277 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.974). Consistent with these predictions, functional studies indicate the variant protein exhibits reduced channel current density and exerts a dominant negative effect on wildtype KCNQ1 (Aidery 2011, Chen 2011). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic and cardiology consultations are indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic KCNQ1 variant (Familial Targeted Sequencing, ARUP test code 3005867).

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

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Aidery et al. Biophysical properties of mutant KCNQ1 S277L channels linked to hereditary long QT syndrome with phenotypic variability. Biochim Biophys Acta. 2011 Apr;1812(4):488-94. PMID: 21241800.
Chen et al. A dual mechanism for I(Ks) current reduction by the pathogenic mutation KCNQ1-S277L. Pacing Clin Electrophysiol. 2011 Dec;34(12):1652-64. PMID: 21895724.
Liu et al. KCNQ1 and KCNH2 mutations associated with long QT syndrome in a Chinese population. Hum Mutat. 2002 Dec;20(6):475-6.PMID: 12442276.
Yagi et al. A challenge for mutation specific risk stratification in long QT syndrome type 1. J Cardiol. 2018 Jul;72(1):56-65. PMID: 29439887.

This result has been reviewed and approved by [redacted]
BACKGROUND INFORMATION: Long QT Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Long QT syndrome (LQTS) is characterized by prolongation of the QTc interval and T-wave abnormalities on electrocardiogram that are associated with tachyarrhythmias, often torsade de pointes. Cardiac events including syncope, ventricular fibrillation, or sudden cardiac death may occur from infancy to middle age but are most common in preteens and young adults. Forms of LQTS associated with additional noncardiac features include Andersen-Tawil syndrome (muscle weakness and distinctive facial features), Timothy syndrome (cutaneous syndactyly, neurodevelopmental and facial features), and Jervell and Lange-Nielsen syndrome (congenital sensorineural hearing loss).

EPIDEMIOLOGY: Prevalence of congenital LQTS is approximately 1 in 2,500.

CAUSE: Pathogenic germline variants in genes associated with LQTS

INHERITANCE: Typically autosomal dominant with incomplete penetrance. Autosomal recessive inheritance for Jervell and Lange-Nielsen syndrome.

PENETRANCE: Variable, influenced by gene involved

CLINICAL SENSITIVITY: 60-75 percent

GENES TESTED: CACNA1C, CALM1*, CALM2, CALM3, KCNE1*, KCNE2*, KCNH2*, KCNJ2, KCNQ1, SCN5A, TRDN
*One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants

(SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a heritable form of LQTS. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
CALM1 (NM_001363670) exon(s) 1

Single exon deletions/duplications will not be called for the following exons: KCNH2 (NM_000238, NM_172056) 6; KCNH2 (NM_001204798, NM_172057) 2; TRDN (NM_006073, NM_001251987, NM_001256020, NM_001256021, NM_001256022) 5; CALM1 (NM_001363670) 1
Duplications may not be called for the following genes: CAV3, KCNE1, KCNE2

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

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Long QT Specimen	22-307-111935	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Long QT Interp	22-307-111935	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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