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Client: ARUP Physician Services
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Salt Lake City, NY 84108
UNITED STATES

Physician: TEST,

Patient: PROD, TRACKEXADD POS

DOB	5/17/1984
Gender:	Female
Patient Identifiers:	546192
Visit Number (FIN):	569122
Collection Date:	5/17/2019 10:22

Exome Sequencing, Familial Control

ARUP test code 2006340

Exome Sequencing, Familial Control

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 Sequencing, Familial Control

RESULT
One likely pathogenic variant was detected in the KCNH2 gene. The American College of Medical Genetics and Genomics (ACMG) recommends reporting likely pathogenic and pathogenic variants that are identified in this gene by whole exome sequencing even though this variant may not be related to the primary indication for testing.

LIKELY PATHOGENIC VARIANT
Gene: KCNH2 (NM_000238.3)
Variant: c.2707G>A; p.Gly903Arg - Heterozygous
Chr7(GRCh37):g.150644952
Frequency: rs199473669; gnomAD: 18 out of 152,292 chromosomes, overall allele frequency 0.01%
Conservation: Highly conserved amino acid (Alamut software v2.11.0)
Computational prediction programs: SIFT: tolerated, PolyPhen-2: benign, MutationTaster: disease causing
Inheritance pattern: Autosomal dominant

One likely pathogenic variant, c.2707G>A; p.Gly903Arg, was detected in the potassium channel, voltage gated eag related subfamily H, member 2(KCNH2) gene, also known as ERG1 and HERG, by massively parallel sequencing and confirmed by Sanger sequencing. This gene encodes the pore-forming subunit of a rapidly activating-delayed rectifier potassium channel that plays an essential role in the final repolarization of the ventricular action potential (MIM:152427).

The p.Gly903Arg variant has been reported in three unrelated patients referred for long QT syndrome genetic testing (Kapplinger 2009). This variant was also identified an individual who experienced sudden death who had a structurally normal heart; circumstances of death were described as possibly related to exercise and paraflu/norovirus (Cann 2016). A family member with prolonged QTc also tested positive for p.Gly903Arg variant (Cann 2016). Additionally, this variant was reportedly identified in an individual who also carried a duplication of

FBN1 exons 45-65 (Brugada 2016). Moreover, p.Gly903Arg variant was also identified in multiple unrelated individuals tested for long QT syndrome at another laboratory (see ClinVar Database link). Thus, based on the available information, we have classified the p.Gly903Arg variant as likely pathogenic.

Pathogenic KCNH2 variants are associated with inherited long QT syndrome 2 and susceptibility to acquired long QT syndrome 2 (MIM:613688) as well as with short QT syndrome 1 (MIM:609620). Long QT syndrome represents a potentially life-threatening cardiac arrhythmia characterized by delayed myocardial repolarization that produces QT prolongation and increased risk for torsades des pointes (TdP)-triggered syncope, seizures, and sudden cardiac death (SCD) in an otherwise healthy young individual with a structurally normal heart (Tester 2014). Of note, pathogenic KCNH2 variants have been identified in patients with sudden unexpected death in epilepsy (Bagnall 2016). However, pathogenic KCNH2 variants have also been detected inasymptomatic individuals with or without prolonged QTc interval (Jimenez-Jaimez 2011; Munoz-Esparza 2015). Thus, KCNH2 carriers may remain asymptomatic throughout their life or the clinical presentation may vary from presyncope to syncope, from ventricular arrhythmias to sudden cardiac death (Murphy and Gill, 2008). Consequently, for relatives of an index patient with a pathogenic KCNH2 variant, targeted variant-specific testing has been recommended even if the individual had normal ECG results, since directed beta-blockade therapy has been proven useful in preventing cardiac events in LQT2 patients (Vyas and Lambiase, 2013).

No additional 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 ACMG genes are included in the background information. These genes are evaluated only to the extent that standard exome sequencing allows.

RECOMMENDATIONS
Cardiology and genetic consultations are indicated, including a discussion of medical screening and management. At-risk family members should be offered targeted testing for the identified likely pathogenic KCNH2 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). If there is clinical suspicion or family history of a genetic condition associated with one of the ACMG-recommended genes analyzed, additional testing of the specific disease-associated gene(s) should be considered as exome sequencing will not identify all causative variants.

REFERENCES
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Cann, F et al.:
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H=High, L=Low, *=Abnormal, C=Critical

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Murphy, C and Gill, J: Long-QT syndrome in a family with a KCNH2 mutation. Heart Metab 2008; 41:30-33.

Tester, DJ et al.: Genetics of long QT syndrome. Methodist Debakey Cardiovascular J 2014; 10(1):29-33.

Vyas, V and Lambiase, PD: The investigation of sudden arrhythmic death syndrome (SADS)-the current approach to family screening and the future role of genomics and stem cell technology. Front Physiol 2013; 4:199.

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

BACKGROUND INFORMATION: Exome Sequencing, Familial Control

CHARACTERISTICS: DNA coding regions and intron/exon boundaries of the human exome are sequenced to identify the cause(s) of a disorder in a family member. The American College of Medical Genetics (ACMG) recommends analysis of the following genes for pathogenic mutations in all individuals undergoing exome sequencing:

GENES ASSOCIATED WITH AN INCREASED RISK FOR TUMORS/CANCER: hereditary breast and ovarian cancer (BRCA1, BRCA2), Li-Fraumeni syndrome (TP53), Peutz-Jeghers syndrome (STK11), Lynch syndrome (MLH1, MSH2, MSH6, PMS2), familial adenomatous polyposis (APC), MUTYH-associated polyposis, Von Hippel Lindau syndrome (VHL), multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2/familial medullary thyroid cancer (RET), PTEN hamartoma tumor syndrome (PTEN), retinoblastoma (RB1), hereditary paraganglioma-pheochromocytoma syndrome (SDHD, SDHAF2, SDHC, SDHB), tuberous sclerosis complex (TSC1, TSC2), WT1-related Wilms (WT1), neurofibromatosis type 2 (NF2). GENES ASSOCIATED WITH CARDIOVASCULAR (HEART) PROBLEMS: EDS IV (COL3A1), Marfan syndrome (FBN1), Loeys-Dietz syndrome (TGFBR1 and TGFBR2), familial thoracic aortic aneurysms and dissections (SMAD3, ACTA2, MYLK, MYH11), hypertrophic cardiomyopathy/dilated cardiomyopathy (MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA ,MYL2, LMNA), catecholaminergic polymorphic ventricular tachycardia (RYR2), arrhythmogenic right ventricular cardiomyopathy (PKP2, DSP, DSC2, TMEM43, DSG2), Romano-Ward long QT syndromes types 1, 2, and 3, Brugada syndrome (KCNQ1, KCNH2, SCN5A), familial hypercholesterolemia (LDLR, APOB, PCSK9).

GENES INFLUENCING RESPONSE TO ANESTHESIA: malignant hyperthermia (RYR1, CACNA1S).

INHERITANCE: Varies depending on the specific gene and variant.

CLINICAL SENSITIVITY: Varies by gene.

METHODOLOGY: Targeted 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 confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

LIMITATIONS OF ANALYSIS: Not all pathogenic variants occur in the coding regions of genes. Some genes, or parts of genes, may not be adequately sequenced to allow for confident analysis. The following types of variants may not be detectable: those located in genes with corresponding pseudogenes, those in repetitive or high GC rich regions, large deletions / duplications / rearrangements, and mosaic mutations. Rare variants in probe hybridization sites may compromise analytical sensitivity. Mode of inheritance, reduced penetrance,and genetic heterogeneity could reduce the clinical sensitivity.

LIMITATIONS OF REPORTING: Only known pathogenic variants identified in genes on the ACMG-recommended panel are reported. Variants of unknown significance will not be reported. Single pathogenic variants in autosomal recessive genes will not be reported.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Exome Sequencing, Familial Control	19-137-104832	5/17/2019 10:22:00 AM	5/17/2019 10:25:23 AM	5/17/2019 1:36:00 PM

END OF CHART

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