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GeneDx Accession Number: 1638665

To: Dr. Kris Cunningham

Forensic Services Technologist

From: Clinical Staff

Fax: 416-314-4060 **Pages:** 6

TEST	Comprehensive Arrhythmia Panel			
FAXED	14-OCT-2016			

GeneDx is going green! As part of our effort to be environmentally responsible, beginning 1/1/2014, GeneDx will no longer send genetic test reports by mail. We will continue to send reports by fax, email or through our electronic reporting system according to your preferences.

If you are interested in an electronic method of report delivery, GeneDx utilizes the CareEvolve reporting system. CareEvolve is a user-friendly, web-based, HIPAA compliant, secure report retrieval system. This method allows for quick electronic access to reports that will help eliminate excess paper copies. Reports are uploaded every hour in a convenient pdf format and can be accessed and retrieved repeatedly.

If you are interested in learning more about the CareEvolve system, please contact our Customer Service Specialist at techsupport@genedx.com.

Thank you,
GeneDx Clinical Staff

Additional tests can be added on most specimens if we receive faxed orders including authorization FROM THE PARTY TO BE BILLED. Physicians, please route your requests through the in-house or local laboratory that handled the initial specimen.

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Cardiology Genetics Report

Patient Name:	**CEYLAN, Raffi**	**GeneDx Accession No:**	**1638665**
Date of Birth:	**05-FEB-1973**	**Date Specimen Obtained:**	**16-JUL-2016**
Specimen Type:	**DNA**	**Date Specimen Received:**	**16-SEP-2016**
Submitters ID No:	**16SA198 MQ, 2v80861**	**Date Test(s) Started:**	**16-SEP-2016**
Ordered By:	**Dr. Kris Cunningham**	**Date of Report:**	**14-OCT-2016**

Test(s) Requested: Comprehensive Arrhythmia Sequencing and Deletion/Duplication Panel

Genes Evaluated: ABCC9, AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, DES, DSC2, DSG2, DSP, GPD1L, HCN4, JUP, KCND3, KCNE1, KCNE2, KCNE3, KCNE1L, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, LMNA, NKX2.5, PKP2, PLN, RANGRF, RYR2, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SNTA1, TGFB3, TMEM43, TRDN, TRPM4, TTN

Result: **SEE INTERPRETATION**

Gene	Coding DNA	Variant	Zygosity	Classification
ANK2	c.3718 C>G	p.Pro1240Ala (P1240A)	Heterozygous	Variant of Uncertain Significance

No definitive pathogenic variants known to be associated with arrhythmia were identified by sequence analysis of the 46 genes on this panel. No deletion or duplication involving any of the 45 genes analyzed was found by concurrent targeted array CGH (ExonArrayDx). The CALM1 gene is not included on the Arrhythmia ExonArrayDx.

Interpretation: **This individual is heterozygous for variant of uncertain significance in the ANK2 gene.**

The Comprehensive Arrhythmia Panel includes sequence and deletion/duplication analysis of genes that cause various arrhythmia syndromes. Many of these genes code for ion channel proteins of the heart muscle that mediate the movement of sodium, potassium and calcium ions in and out of cardiac cells, as well as their associated regulatory factors and interaction partners. There are several different genetic arrhythmia disorders. Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) affects the cardiac desmosome, which is a protein complex that maintains cell-to-cell connections and provides mechanical attachments between adjacent cells. ARVC is characterized by myocyte death and replacement by fat and fibrous tissue in the right ventricle, predisposing to ventricular tachyarrhythmia and sudden cardiac death (McNally et al., 2014; Nava et al., 2000). Brugada syndrome (BrS) is caused by abnormal ion channel function and is characterized by ST segment elevation on ECG (leads V1-3) in the absence of structural heart disease. BrS is associated with increased risk for syncope, ventricular tachyarrhythmia and sudden cardiac death (Fowler et al., 2009; Hedley et al., 2009; Brugada et al., 2014). Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by cardiac calcium channel dysfunction that is precipitated by stress-induced release of catecholamines (de la Fuente et al., 2008; Priori et al., 2002). Long QT syndrome (LQTS) is characterized by prolongation of the QT interval on ECG and is associated with increased risk for syncope, ventricular arrhythmia, and sudden cardiac death in individuals with normal heart structure (Goldenberg et al., 2008; Priori et al., 2004; Alders and Christiaans, 2015; Tranebjaerg et al., 2014). Genetic predisposition to a cardiac arrhythmia may occur as an isolated feature or may be part of a multisystemic disorder, such as Jervell and Lange-Nielsen syndrome, Timothy syndrome, Andersen-Tawil syndrome, Naxos disease, Carvajal syndrome and muscular dystrophy.

ANK2 Summary: The ANK2 gene is a member of the ankyrin protein family, which play a role in cell motility, activation, proliferation, contact, and maintenance of specialized membrane domains (MIM: 106410). Heterozygous pathogenic variants in ANK2 have been reported in association with Long QT syndrome (LQTS) (Mohler et al., 2003).

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ANK2 p.P1240A:

p.Pro1240Ala (P1240A) (CCC>GCC): c.3718 C>G in exon 31 of the ANK2 gene (NM_001148.4)

A variant of uncertain significance has been identified in the ANK2 gene. The P1240A variant has not been published as a pathogenic variant, nor has it been reported as a benign variant to our knowledge. This variant was not observed in approximately 6,500 individuals of European and African American ancestry in the NHLBI Exome Sequencing Project, indicating it is not a common benign variant in these populations. The P1240A variant is a semi-conservative amino acid substitution, which may impact secondary protein structure as these residues differ in some properties. This substitution occurs at a position that is conserved across species and in silico analysis predicts this variant is probably damaging to the protein structure/function. However, to our knowledge no studies have been performed to determine the functional effect of the P1240A variant.

Therefore, based on the currently available information, it is unclear whether this variant is pathogenic or benign. This result cannot be interpreted for diagnosis or used for family member screening at this time.

Recommendation:

1. It is recommended that any first-degree relatives receive continued clinical evaluation and follow-up.

2. Targeted testing of affected relatives could be considered to determine if the P1240A variant in the ANK2 gene segregates with disease in this family. If there are no affected relatives, targeted testing of this individual's parents could be considered to determine if the variant occurred de novo. Cumulative data about this variant, including multiple instances of segregation with disease and/or de novo occurrence may assist in further variant interpretation and classification.

3. Genetic counseling is recommended to discuss the implications of this test report, specifically the risk of recurrence for this family.

Resources:

Patients willing to share their genetic and health data (de-identified for privacy) to advance knowledge and to connect with others with the same variant/condition can visit genomeconnect.org.

Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the 46 genes (Only exons 1-44 for CACNA1C, only the KCNQ1-binding domains including Ser1570 residue for AKAP9, and excluding exon 6 of the PKP2 gene and the following genomic regions of the TTN gene: chr2:179527692-179527782, 179523898-179523982, 179523731-179523815) are enriched using a proprietary targeted capture system developed by GeneDx. These targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads are achieved by NextGen sequencing. Concurrent deletion/duplication testing was performed using exon-level oligo array CGH (ExonArrayDx) for most of the coding exons of the requested genes, except for CALM1. KCNE1L and SCN1B have gene level resolution; exon level events may not be detected. Data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. The array is designed to detect most intragenic deletions and duplications. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat array CGH analysis. Sequence and array CGH alterations are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Benign and likely benign variants, if present, are not included in this report but are available upon request.

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Supplemental Variant Information:

Gene: Coding DNA	**ANK2: c.3718 C>G**
Variant (Protein)	p.Pro1240Ala (P1240A)
Classification	Variant of Uncertain Significance
Zygosity	Heterozygous
Chr: Position	4: 114257859
dbSNP	
1000G	
1000G_Highest	
1000G_Highest_Sub	
ExAC_Freq	
ExAC_Latino	
ExAC_NFE	
ExAC_AFR	
ExAC_EAS	
ExAC_FIN	
ExAC_Other	
ExAC_SAS	
ExAC_Hom	
PROVEAN	
MutTaster_Score	1 (D)
Interpro_Domain	
ClinVar	

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This supplement provides evidence to support the classification of each reportable variant in the attached result report. This information is provided as a resource and may not be inclusive of all available information used by GeneDx for variant classification. The variant classification does not rely solely on any one of the individual criterion provided below. In addition, each criterion is weighted differently to derive the classification. This information is subject to change over time and may differ from what is currently available. This supplement is provided upon request to ordering providers. GeneDx has already conducted a thorough analysis of the data at the time testing was ordered and does not provide additional support to providers who have questions about the tools used in variant analysis and interpretation for a specific case. Results should always be interpreted in the context of the patient's clinical presentation.

Blank fields indicate that no data was available at time of analysis.

Data from the 1000 Genomes Project has been modified by GeneDx to exclude related individuals. For more information about the specific populations included in the 1000 Genomes Project, please see http//www.1000genomes.org (McVean et al., 2012).

The Exome Aggregation Consortium (ExAC) provides a beta-version of a set of exome sequencing data from a variety of large-scale sequencing projects (Lek et al., 2016). The ExAC set includes data from individuals who were recruited for disease-specific studies, including cancer and cardiovascular diseases. Genotype quality metrics and site quality metrics for a specific variant are available at http://exac.broadinstitute.org.

REFERENCES:

1. 1000 Genomes Project: McVean et al. (2012) Nature 491 (7422):56-65 (PMID: 23128226). 2. ExAC: Lek et al. (2016) Nature 536 (7616):285-91 (PMID: 27535533). 3. PROVEAN: Choi et al. (2012) PLoS ONE 7 (10):e46688 (PMID: 23056405). 4. Mutation Taster: Schwarz et al. (2014) Nature methods 11 (4):361-2 (PMID: 24681721). 5. CADD: Kircher et al. (2014) Nature Genetics 46 (3):310-5 (PMID: 24487276). 6. Interpro: Mitchell et al. (2015) Nucleic Acids Res. 43 (Database issue):D213-21 (PMID: 25428371). 7. ClinVar: Landrum et al. (2014) Nucleic Acids Res. 42 (1):D980-5 (PMID: 24234437).

Frequency/Catalog Information

dbSNP - NCBI repository for single base nucleotide substitutions and short deletion and insertion polymorphisms

1000G - Variant allele frequency among 2500 individuals included in the 1000 Genomes project, a catalog of human genetic sequence variation obtained through genomic sequencing (Percent values in parentheses)

1000G_Highest - Highest reported percentage frequency of a variant in any 1000G sub-population

1000G_Highest_Sub - Sub-population referenced in 1000G_Highest (AMR=Admixed American, EAS=East Asian, SAS=South Asian, AFR=African, EUR=European)

ExAC_Freq - Variant allele frequency among approximately 60,000 individuals included in the Exome Aggregation Consortium (ExAC) dataset, a catalog of human genetic sequence variation obtained through exome sequencing (Percent values in parentheses)

ExAC_Latino - ExAC variant frequency (in percent) for individuals of Latino ancestry

ExAC_NFE - ExAC variant frequency (in percent) for non-Finnish individuals of European ancestry

ExAC_AFR - ExAC variant frequency (in percent) for individuals of African ancestry

ExAC_EAS - ExAC variant frequency (in percent) for individuals of East Asian ancestry

ExAC_FIN - ExAC variant frequency (in percent) for Finnish individuals of European ancestry

ExAC_Other - ExAC variant frequency (in percent) for individuals of other ancestry

ExAC_SAS - ExAC variant frequency (in percent) for individuals of South Asian ancestry

ExAC_Hom - The number of individuals in ExAC who are homozygous for the variant

Information on Prediction Scores

PROVEAN (Protein Variation Effect Analyzer) - predicts whether an amino acid substitution or indel affects the biological function of a protein using a delta alignment score from -14 to +14 (more negative=more damaging) with a predefined threshold of -2.5. If the PROVEAN score is equal to or below -2.5, the variant is predicted to have a deleterious effect. If the PROVEAN score is greater than -2.5, the variant is predicted to have a neutral effect.

MutTaster_Score - Represents the strength of the calculation matching a simple, automated prediction based on population statistics and ClinVar data (Example: A high-scoring variant may be both calculated to be damaging and has a 'damaging' flag in ClinVar.) A high score does NOT indicate a high probability of accuracy. Predictions (in parentheses) are: 'A' - Disease-causing Automatic (known pathogenic), 'D' - Disease-causing, 'N' - Polymorphism, 'P' - Polymorphism Automatic (known benign).

Note that the in silico scores used by GeneDx are precomputed and may change over time. In silico models use algorithms that predict the effect a variant may have on the protein, but they do not provide direct evidence regarding the actual impact on protein structure or function. In silico models should be interpreted with caution and only be used in combination with other available evidence to support the classification of any variant. CADD (Combined Annotation Dependent Depletion) is also used by GeneDx to evaluate the deleterious effect of a single nucleotide variant (SNV) or indel.

Interpro_Domain - Domain annotations come from the Interpro database. The number in parentheses reflects how many times Interpro has assigned the variant position to that domain, typically derived from different predicting databases.

ClinVar - Classification of variant in ClinVar database, an NCBI archive of human variants with supporting evidence of phenotypic association.

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Report electronically signed by:
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Mohler et al. (2003) Nature 421 (6923):634-9 (PMID: 12571597)

Exome Variant Server, NHLBI Exome Sequencing Project (ESP), Seattle, WA (URL: http://evs.gs.washington.edu/EVS/) [9/2016 accessed]

Limitations: Genetic testing using the methods applied at GeneDx is expected to be highly accurate. Normal findings do not rule out the diagnosis of a genetic disorder since some genetic abnormalities may be undetectable with this test. Neither sequencing nor exon-level array CGH can reliably detect mosaicism and/or chromosomal aberrations. Deletions/insertions of 5 bp or more are not reliably detected by the NextGen sequencing methodology and deletions/insertions of less than 500 bp are not reliably detected by array CGH. Rarely incidental findings of large chromosomal rearrangements (>3Mb) outside the gene of interest may be identified. Some genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that may result in suboptimal data, and variants in those regions may not be reliably identified. False negative results may also occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. The chance of a false positive or false negative result due to laboratory errors incurred during any phase of testing cannot be completely excluded. Interpretations are made with the assumption that any information provided on family relationships is accurate. Consultation with a genetics professional is recommended for interpretation of results.

Disclaimer: This test was developed and its performance characteristics determined by GeneDx. It has not been cleared or approved by the U.S. Food and Drug Administration. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.