Phosphorus Diagnostics

CARDIOLOGY

PERFORMED AT PHOSPHORUS DIAGNOSTICS,
400 PLAZA DRIVE, SUITE 401, SECAUCUS, NJ 07094

ORDERING PRACTICE

Practice Code: 100
Sample Cardiology Clinic
374 Broadway
New York, NY 10001
Physician: Dr. Sample

JANE DOE

DOB: 1973-02-19
Gender: Female
Ethnicity: European
Procedure ID: 87000
Kit Barcode: 201612092248585
Specimen: Blood, #10000
Specimen Collected: 2016-01-12
Specimen Received: 2016-01-13
Specimen Analyzed: 2016-01-21
Report Generated: 2016-02-03

TEST INFORMATION

Panel: Pan Arrhythmia and Cardiomyopathy Panel
Indication: Diagnostic for Patient History

SUMMARY OF RESULTS

Positive: Pathogenic Variant Identified

GENE	LOCATION	VARIANT	INHERITANCE	ZYGOSITY	CLASSIFICATION
KCNQ1	Exon 6; Chrom 11	c.914G>A (p.Trp205Ter)	Autosomal Dominant	Heterozygous	**PATHOGENIC**
MYH7	Exon 38; Chrom 14	c.26647G>A (p.Glu1883Lys)	Unknown	Heterozygous	UNCERTAIN SIGNIFICANCE

INTERPRETATION

This patient is heterozygous for the c.914G>A (p.Trp205Ter) pathogenic variant in KCNQ1.

This result indicates that this patient may be affected with, or predisposed to developing, long QT syndrome.

This patient is also heterozygous for the c.185G>A (p.Lys65Ala) variant of unknown clinical significance in MYH7. The contribution of this variant to the patient's phenotype is unknown.

RECOMMENDATIONS

Clinical follow-up with a cardiologist or cardiogeneticist is recommended to discuss medical management.

Genetic counseling is recommended for this patient.

Genetic testing may be useful in identifying family members at risk for disease. Genetic counseling is recommended for all individuals undergoing genetic testing.

VARIANT INFORMATION

PATHOGENIC

KCNQ1 c.914G>A (p.Trp305Ter)

This variant leads to a premature termination at codon 305, which is expected to result in an absent or significantly disrupted protein product. Variants resulting in truncations have been previously reported in long QT Syndrome. This mutation does not appear in large population databases, indicating it is not a common variant. This variant has been shown to segregate with disease in one family with long QT syndrome (PMID: 12702160). Therefore, this variant is classified as pathogenic.

GENE INFORMATION: KCNQ1

The KCNQ1 gene encodes the potassium voltage-gated channel subfamily KQT member 1 protein which is involved in the regulation of action potentials within cardiac tissue, which control cardiac contraction. Mutations in KCNQ1 are associated with autosomal dominant long QT syndrome (MIM: 192500), short QT syndrome (MIM: 609621), atrial fibrillation (MIM: 607554) and autosomal recessive Jervell and Lange-Nielsen syndrome (MIM: 220400). Mutations in KCNQ1 are responsible for ~40% of long QT syndrome PMID(19716085).

UNCERTAIN SIGNIFICANCE

MYH7 c.26647G>A (p.Glu1883Lys)

This variant has been reported in a homozygous state in a 44 year old man with hypertrophic cardiomyopathy and myopathy. The parents were unaffected heterozygous carriers. (PMID: 17372140). Other mutations that have been associated with myopathy and hypertrophic cardiomyopathy have been identified in this region (Arg 1845Trp and Glu1886Lys) which supports the functional importance of this protein region (PMID: 14520662, PMID: 19336582) . This variant does not appear in population databases, including Exac. Polyphen in silico analysis predicts the variant to be "probably damaging." In summary, there is inconclusive evidence to determine whether this is a damaging, pathogenic variant or benign, rare variant-therefore, at this time this variant has been determined to be a variant of unknown significance.

GENE INFORMATION: MYH7

The MYH7 gene encodes the myosin heavy chain 7 protein which is involved in cardiac muscle contraction. Mutations in MYH7 are associated with autosomal dominant hypertrophic cardiomyopathy (OMIM ID: 192600), dilated cardiomyopathy (OMIM ID: 613426), left ventricular noncompaction (OMIM ID: 613426), autosomal dominant and recessive myosin storage myopathy (OMIM ID: 608358, 255160), and other disorders (OMIM: 160500, 181430).

CLIA #31D2123554

METHODS

SEQUENCING

Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization based protocol and sequenced using Illumina technology. Reads are aligned to the reference sequence (Grch37, standard genome build hg19), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript. Exonic deletions and duplications are called using a copy number variation (CNV) algorithm. The CNV algorithm calculates a statistical likelihood of each copy number state by comparing the depth of sequencing coverage at targeted exons to a baseline depth measure in control samples. A confidence threshold is used for each assertion of copy number state for each exon where the sequence data met a minimum quality standard of ≥ 20x depth of unique properly paired reads. This algorithm detects most intragenic deletions and duplications, although rare single-exon events may be missed.

The analytical sensitivity and specificity of this assay is 99.5% and 99.9%, respectively. All reportable variants are confirmed by orthogonal technologies as part of our ongoing quality management process. Unless otherwise indicated, all targeted regions were sequenced with ≥ 20x depth of coverage. Regions with a read depth below this are supplemented with orthogonal testing, if they contain previously reported pathogenic variants. The assay targets all coding regions of the indicated transcript, 10 base pairs of flanking intronic sequence, and specific intronic and intragenic genomic regions demonstrated to be causative of disease. However, for some genes only targeted loci are analyzed.

Phosphorus can be contacted via phone at 1-855-746-7423 or by email at support@phosphorus.com

LIMITATIONS

Although this test is highly accurate, no genetic test is 100% sensitive. This analysis is designed to detect pathogenic variants within the coding regions of genes included in the current panel that are associated with specific forms of hereditary cardiovascular disease. Hence this analysis will not detect novel sequence variants in the promoter region and other non-coding regions, as well as it does not assay untranslated exons. Also, the sensitivity to detect insertions and deletions larger than 15 base pairs but smaller than a full exon may be reduced. Some exons of a few individual genes have inherent sequence properties that yield suboptimal data, and pathogenic variants in those regions may not be reliably identified. The low-level mosaicism will not be detected. Moreover, this analysis does not detect every pathogenic variant associated with this disease because of genes not included in the current panel or unknown to be associated with the disease at this time. It also does not test for all known genetic diseases. Errors in testing (both false positives and false negatives) may also occur for reasons that include, but are not limited to specimen issues (e.g. inaccurately marked samples causing sample mix-up, DNA quality and quantity not meeting minimum requirements), rare genetic variants interfering with analysis, assay technical limitations, biological factors (e.g. recent blood transfusions, circulating hematolymphoid neoplasm, or history of bone marrow transplantation), and other technical issues.

If a pathogenic variant is detected, the patient may be a carrier of, affected with, predisposed to, or at risk for certain disease(s) or condition(s) associated with that variant. If no pathogenic variant is found, the patient may be at reduced risk of being a carrier of, affected with, predisposed to, or at risk for the disease(s) or condition(s) tested for in the current panel. However, further testing may be necessary, since negative test results may reduce, but do not eliminate, the chance that the patient is a carrier of, affected with, predisposed to, or at risk of having said disease(s) or condition(s). In addition, other pathogenic variant(s) or factors that are not included in our services may impact an individual's risk of or predisposition to certain disease(s) or condition(s). Thus, this report does not provide definitive conclusions regarding risk of, predisposition to, or diagnosis of certain disease(s) or condition(s).

Variants classified as likely benign or benign are not included in this report, but are available upon request. The possibility that these variants contribute to disease cannot be excluded.

As new information becomes available, variant classification may evolve over time. Providers are encouraged to contact support@phosphorus.com to obtain updated information.

DISCLAIMER

This report reflects the analysis of an extracted DNA sample; and it does not constitute medical advice. Any questions or concerns regarding the contents of this report or any prevention, cure, mitigation, or treatment of a medical condition or disease should be directed to a qualified cardiologist, cardio-geneticist, or genetic counselor.

This test was developed and its performance characteristics determined by Phosphorus Diagnostics, LLC. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test results are to be used for clinical purposes and should not be regarded as investigational or for research.

VARIANT CLASSIFICATION

All variants that are identified in the sequenced genes and determined to be pathogenic, likely pathogenic, of uncertain significance are reported. Variants determined to be likely benign or benign are not reported, but are available upon request. Variants are classified in accordance with ACMG guidelines (PMID: 25741868).

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GENES ASSAYED

A2ML1	NM_144670
ABCC9	NM_020297
ACADVL	NM_000018
ACTC1	NM_005159
ACTN2	NM_001103
AGL	NM_000642
AKAP9	NM_005751
ALMS1	NM_015120
ANK2	NM_001148
ANKRD1	NM_014391
BAG3	NM_004281
BRAF	NM_004333
CACNA1C	NM_199460
CACNA2D1	NM_000722
CACNB2	NM_201596
CALM1	NM_006888
CALM2	NM_001743
CALM3	NM_005184
CALR3	NM_145046
CASQ2	NM_001232
CAV3	NM_033337
CBL	NM_005188
CHRM2	NM_001006632
CPT2	NM_000098
CRYAB	NM_001885
CSRP3	NM_003476
CTF1	NM_001330
CTNNA3	NM_013266
DES	NM_001927
DMD	NM_004006
DNAJC19	NM_145261
DOLK	NM_014908
DSC2	NM_024422
DSG2	NM_001943
DSP	NM_004415
DTNA	NM_001390
ELAC2	NM_001165962
EMD	NM_000117
EYA4	NM_172105
FHL1	NM_001159702
FHL2	NM_001450
FKRP	NM_001039885
FKTN	NM_006731
FLNC	NM_001458
GAA	NM_001079804
GATA4	NM_002052
GATA6	NM_005257
GATAD1	NM_021167
GLA	NM_000169
GPD1L	NM_015141
HCN4	NM_005477
HRAS	NM_001130442
ILK	NM_004517
JPH2	NM_020433
JUP	NM_002230
KCND3	NM_004980
KCNE1	NM_001127670
KCNE2	NM_172201
KCNE3	NM_005472
KCNE1L	NM_012282
KCNH2	NM_000238
KCNJ2	NM_000891
KCNJ5	NM_000890
KCNJ8	NM_004982
KCNQ1	NM_000218
KRAS	NM_033360
LAMA4	NM_001105206
LAMP2	NM_001122606
LDB3	NM_007078
LMNA	NM_170707
LRRC10	NM_201550
MAP2K1	NM_002755
MAP2K2	NM_030662
MTO1	NM_133645
MYBPC3	NM_000256
MYH6	NM_002471
MYH7	NM_000257
MYL2	NM_000432
MYL3	NM_000258
MYLK2	NM_033118
MYOM1	NM_003803
MYOZ2	NM_016599
MYPN	NM_001256267
NEBL	NM_006393
NEXN	NM_144573
NF1	NM_001042492
NKX2-5	NM_004387
NPPA	NM_006172
NRAS	NM_002524
PDLIM3	NM_014476
PKP2	NM_004572
PLEKHM2	NM_015164
PLN	NM_002667
PRKAG2	NM_016203
PTPN11	NM_002834
RAF1	NM_002880
RANGRF	NM_016492
RASA1	NM_002890
RBM20	NM_001134363
RIT1	NM_001256821
RRAS	NM_006270
RYR2	NM_001035
SCN1B	NM_199037
SCN2B	NM_004588
SCN3B	NM_018400
SCN4B	NM_174934
SCN5A	NM_001160161
SCN10A	NM_006514
SDHA	NM_004168
SGCD	NM_001128209
SHOC2	NM_007373
SLC22A5	NM_003060
SLMAP	NM_007159
SNTA1	NM_003098
SOS1	NM_005633
SOS2	NM_006939
SPRED1	NM_152594
TAZ	NM_000116
TCAP	NM_003673
TGFB3	NM_003239
TMEM43	NM_024334
TMEM70	NM_017866
TMPO	NM_003276
TNNC1	NM_003280
TNNI3	NM_000363
TNNT2	NM_001276345
TPM1	NM_001018020
TRDN	NM_006073
TRPM4	NM_017636
TTN	NM_001256850
TTR	NM_000371
TXNRD2	NM_006440
VCL	NM_014000

PANEL INFORMATION: PAN ARRHYTHMIA AND CARDIOMYOPATHY PANEL

The Pan Arrhythmia and Cardiomyopathy Panel is a comprehensive next-generation (NGS) panel that can be used to confirm a clinical diagnosis of arrhythmia and/or cardiomyopathy or identify at-risk individuals.

Arrhythmias are abnormal heart rhythms, and can be caused by problems with the heart's electrical system or structural problems within the heart. Arrhythmias may be asymptomatic, and only detectable on ECG or other cardiac tests, or may cause symptoms such as syncope, shortness of breath, and heart palpitations. In some cases, arrhythmias can lead to cardiac arrest and sudden cardiac death, even in the absence of prior symptoms. The most common hereditary arrhythmias are long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome. The disorders may show clinical overlap, and demonstrate allelic and locus heterogeneity.

Cardiomyopathy is a disease of the heart muscle that can cause the heart to become weak, rigid, enlarged, or thickened. Cardiomyopathy can lead to irregular heart beats, progressive heart failure, or sudden cardiac death. There are many forms of cardiomyopathy, some of which are acquired and some of which are inherited. The most common hereditary cardiomyopathies include hypertrophic cardiomyopathy, dilated cardiomyopathy, left ventricular noncompaction, arrhythmogenic right ventricular cardiomyopathy, and restrictive cardiomyopathy. The disorders may show significant clinical overlap, and demonstrate allelic and locus heterogeneity.

PREVALENCE

The prevalence of the various forms of arrhythmias and cardiomyopathies are:

- Long QT syndrome: 1/2,000 (PMID: 19121811)
- Short QT syndrome: Unknown
- Catecholaminergic polymorphic ventricular tachycardia: 1/10,000 (PMID: 23549275)
- Brugada syndrome: 1/2,000 (PMID: 18054807)
- Dilated cardiomyopathy: 1/2,700 (PMID: 2766509)
- Left ventricular noncompaction: 1/500 to 1/2,000 (PMID: 27448685)
- Arrhythmogenic right ventricular cardiomyopathy: 1/1000 to 1/1,250 (PMID: 16737750)
- Restrictive cardiomyopathy: Unknown (rare)
- Hypertrophic cardiomyopathy: 1/200 to 1/500 (PMID: 25814232)

INHERITANCE AND PENETRANCE

Hereditary arrhythmias and cardiomyopathies are typically inherited in an autosomal dominant manner, although some of the conditions on the panel are inherited in an autosomal recessive or X-linked manner.

Autosomal Recessive:

- Jervell Lange-Nielsen syndrome
- TRDN and CASQ2-related CPVT
- Naxos disease
- Pompe disease
- Emery-Dreifuss muscular dystrophy
- Primary carnitine deficiency
- Glycogen storage disease type IIIa/b
- FKTN and FKRP muscular dystrophy-dystroglycanopathies
- Emery-Dreifuss muscular dystrophy

X-linked:

- Emery-Dreifuss muscular dystrophy
- Barth syndrome
- Danon disease
- Duchenne muscular dystrophy
- Fabry disease

INCLUDED DISORDERS

This panel includes genes associated with:

- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Left ventricular noncompaction
- Restrictive cardiomyopathy
- Danon disease
- Duchenne and Becker muscular dystrophy
- Emery-Dreifuss muscular dystrophy
- Other disorders
- Long QT syndrome
- Short QT syndrome
- Catecholaminergic polymorphic ventricular tachycardia
- Brugada syndrome
- Arrhythmogenic cardiomyopathy
- Andersen-Tawil syndrome
- Timothy syndrome
- Fabry disease
- Myofibrillar myopathy
- Wolff-Parkinson-White syndrome
- Barth syndrome
- Jervell Lange-Nielsen syndrome
- Timothy syndrome
- Transthyretin amyloidosis

CLINICAL SENSITIVITY

The clinical sensitivity of this test is dependent on the patient's phenotype. In general, the clinical sensitivity for each condition is listed below:

- Long QT syndrome: 80% (PMID: 21787999)
- Short QT syndrome: Unknown
- Brugada syndrome: 15-30% (PMID: 20129283)
- Hypertrophic cardiomyopathy: 60% (PMID: 22068435)
- Dilated cardiomyopathy: 40% (PMID: 23900355)
- Left ventricular noncompaction: 20-40% (PMID: 18506004; 20530761)
- Arrhythmogenic right ventricular cardiomyopathy: 50% (PMID: 21606390)
- Restrictive cardiomyopathy: ~35% (PMID: 23274168)

SIGNED BY

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