Phosphorus Diagnostics

OPHTHALMOLOGY

PERFORMED AT PHOSPHORUS DIAGNOSTICS,
400 PLAZA DRIVE 4TH FLOOR SUITE 301, SECAUCUS, NJ 07094

ORDERING PRACTICE

Practice Code: 100
Sample Eye 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 Retinal Disorders Panel
Indication: Diagnostic for Patient History

SUMMARY OF RESULTS

Positive: Pathogenic Variant Identified

GENE	LOCATION	VARIANT	INHERITANCE	ZYGOSITY	CLASSIFICATION
RHO	Exon 2; Chrom 3	c.404_405delGGinsTT (p.Arg135Leu)	Autosomal Dominant	Heterozygous	**PATHOGENIC**
CEP290	Exon 38; Chrom 14	c.226G>A (p.Ala76Thr)	Unknown	Heterozygous	UNCERTAIN SIGNIFICANCE

INTERPRETATION

This patient is heterozygous for the c.404_405delGGinsTT (p.Arg135Leu) pathogenic variant in RHO.

This result indicates that this patient may be affected with, or predisposed to developing, retinitis pigmentosa.

This patient is also heterozygous for the c.226G>A (p.Ala76Thr) variant of unknown significance in CEP290. The contribution of this variant to this patient's phenotype is unknown.

RECOMMENDATIONS

Clinical follow-up 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

RHO c.404_405delGGinsTT (p.Arg135Leu)

This variant leads to an amino acid change from arginine to leucine at codon 135. This amino acid change occurs at a conserved position, and in silico analyses predict this variant to be to be damaging. This variant was identified in 2 of 161 unrelated probands with adRP, and segregated with disease in the families of both probands (PMID:1862076). A different amino acid change at this same position R135W is also reported as pathogenic, and functional analysis of this variant indicates that this variant is disease-causing (PMID:1862076, 1924344). For these reasons, this variant is classifed as pathogenic.

GENE INFORMATION: RHO

The RHO gene encodes the rhodopsin protein which is a photoreceptor required for image formation. Mutations in RHO are associated with autosomal dominant and recessive retinitis pigmentosa (MIM:613731), autosomal dominant and recessive retinitis punctata albescens (MIM:136880), and autosomal dominant congenital stationary night blindness (MIM:610445).

UNCERTAIN SIGNIFICANCE

CEP290 c.226G>A (p.Ala76Thr)

This variant leads to an amino acid change from alanine to threonine at codon 76. This variant occurs at a moderately conserved residue, and in silico predictions of pathogenicity are not concordant. This variant occurs in population databases at a frequency of .09% and has not been reported in the literature in association with disease. In summary, this is a rare missense variant whose impact on protein function is unknown. Therefore, this variant is classified as a variant of uncertain significance.

GENE INFORMATION: CEP290

The CEP290 gene encodes the centrosomal protien of 290 kDa which is involved in the formation and function of cilia. Mutations in CEP290 are associated with autosomal recessive Leber congenital amaurosis (MIM:611755), Joubert syndrome (MIM:610188), and Bardet-Biedl syndrome (MIM:615991).

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% and >99% 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.

All data is processed and analyzed using Elements Software Version 1.

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 ophthalmologic 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 ophthalmologist, medical 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. These 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

ABCA4	NM_000350
ABHD12	NM_001042472
AIPL1	NM_001033054
ARL6	NR_103511
BBS1	NM_024649
BBS2	NM_031885
BEST1	NR_134580
C2ORF71	NM_001029883
C8ORF37	NM_177965
CA4	NM_000717
CDHR1	NM_001171971
CEP290	NM_025114
CERKL	NR_027690
CLRN1	NR_046380
CNGA1	NM_000087
CNGB1	NM_001135639
CRB1	NR_047563
CRX	NM_000554
CYP4V2	NM_207352
DHDDS	NM_001319959
DHX38	NM_014003
EMC1	NM_001271429
EYS	NM_001292009
FAM161A	NR_037710
FLVCR1	NM_014053
FSCN2	NM_012418
GUCA1B	NM_002098
GUCY2D	NM_000180
HGSNAT	NM_152419
HK1	NM_033496
IDH3B	NM_174855
IFT140	NM_014714
IFT172	NM_015662
IMPDH1	NM_001304521
IMPG2	NM_016247
KIAA1549	NM_020910
KIZ	NM_018474
KLHL7	NR_033329
LCA5	NM_181714
LRAT	NM_001301645
MAK	NR_134936
MERTK	NM_006343
MVK	NM_001301182
NEK2	NM_001204182
NMNAT1	NM_001297779
NR2E3	NM_014249
NRL	NM_006177
PDE6A	NM_000440
PDE6B	NM_001145291
PDE6G	NR_026872
PRCD	NR_033357
PROM1	NM_001145848
PRPF3	NM_004698
PRPF31	NM_015629
PRPF6	NM_012469
PRPF8	NM_006445
PRPH2	NM_000322
RBP3	NM_002900
RDH12	NM_152443
RGR	NM_001012720
RHO	NM_000539
RLBP1	NM_000326
ROM1	NM_000327
RP1	NM_006269
RP2	NM_006915
RP9	NM_203288
RPE65	NM_000329
RPGR	NM_000328
RPGRIP1	NM_020366
SAG	NM_000541
SEMA4A	NM_001193302
SLC7A14	NM_020949
SNRNP200	NM_014014
SPATA7	NM_001040428
SPP2	NM_006944
TOPORS	NM_001195622
TRNT1	NM_001302946
TTC8	NM_001288783
TULP1	NM_001289395
USH2A	NM_007123
WDR19	NM_001317924
ZNF408	NM_024741
ZNF513	NM_001201459

PANEL INFORMATION: PAN RETINAL DISORDERS PANEL

The Pan Retinal Disorders Panel is a comprehensive next-generation sequencing (NGS) panel that can be used to confirm a clinical diagnosis of an inherited retinal disorder or identify at-risk individuals.

Retinal disorders are a heterogenous group of disorders that affect the retina, which can lead to vision loss, night blindness, loss of color vision, or blindness. Retinal disorders may be present from birth or progress with age. The most common inherited retinal disorders include achromatopsia, Bardet-Biedl syndrome, cone-rod dystrophy, congenital stationary night blindness, Leber congenital amaurosis, macular dystrophy, retinitis pigmentosa, and Usher syndrome. Retinal disease may occur in isolation or be part of a syndromic condition. These disorders show significant clinical overlap, and demonstrate allelic and locus heterogeneity.

PREVALENCE

The prevalences of the various forms of inherited retinal disorders are:

- Achromatopsia: 1/30,000 (PMID:20301591)
- Bardet-Biedl syndrome: 1/100,000 (PMID:20301537)
- Cone-rod dystrophy: 1/40,000 (PMID: 17270046)
- Congenital stationary night blindness: Unknown
- Leber congenital amaurosis: 1/30,000-1/50,000 (PMID:20301475)
- Macular dystrophy: ~1/8,000 for Stargardt disease (PMID: 20633576)
- Retinitis Pigmentosa: 1/3,500 -1/4000 (PMID:11921605)
- Usher syndrome: 1/6,000 (PMID:20613545)

INHERITANCE

Inherited retinal disorders are inherited in autosomal dominant, autosomal recessive, and X-linked fashions.

INCLUDED DISORDERS

This panel includes genes associated with:

- Achromatopsia
- Bardet-Biedl Syndrome
- Cone-rod dystrophy
- Congenital stationary night blindness
- Leber congenital amaurosis
- Macular dystrophy
- Retinitis pigmentosa
- Senior-Loken syndrome
- Joubert syndrome
- Retinitis punctata albescens
- Vitelliform macular dystrophy
- Stargardt disease
- Oguchi disease
- Newfoundland Rod-cone dystrophy
- Best vitelliform macular dystrophy
- Enhanced S-cone syndrome
- Juvenile retinoschisis
- Choroidal dystrophy
- Short-rib thoracic dysplasia
- Jalili syndrome
- Usher Syndrome

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:

- Achromatopsia: 75-90% (PMID: 23486539)
- Bardet-Biedl syndrome: ~77% (PMID:20301537)
- Cone-rod dystrophy: ~50% (PMID: 17270046)
- Congenital stationary night blindness: 93% (PMID:23714322)
- Leber congenital amaurosis: 50-70% (PMID:25685757)
- Macular dystrophy: ~80% for Stargardt disease (PMID: 11726554)
- Usher syndrome: 90% (PMID: 21697857)
- Retinitis pigmentosa: ~70% for dominant RP, ~30% for recessive RP, ~90% for X-linked RP (PMID:23701314)

SIGNED BY

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