Phosphorus Diagnostics

CARRIER SCREENING

DEMO
400 PLAZA DRIVE, SECAUCUS, NJ, 07094

ORDERING PRACTICE
Carrier Screening Clinic
1140 Broadway, 11th Floor, New York, New York [NY], 10001
Ordering Practitioner: Carrie Screener

TEST ORDER
Report: Expanded Carrier Screen (P15DX.CSFD1.CGG.V1)
Panel: Expanded Carrier Screen - Full Panel
Date Ordered: 2019-02-24

PATIENT
Patient: CS Patient 6
Gender: Male
DOB: 1987-07-09
Ethnicity: Mediterranean, European
Procedure ID: 142864
Kit Barcode(s): 20190224127208
Specimen: Saliva
Specimen Collected:
Specimen Received: 2019-02-24
Generated: 2019-03-01 22:41:36 UTC

PARTNER
Partner: CS Patient 5
Gender:
DOB: 1987-07-08
Ethnicity: N/A
Procedure ID: 142863
Kit Barcode(s): 20190224668945
Specimen: Blood
Specimen Collected:
Specimen Received: 2019-02-24
Report Status: Available

Summary of Results

Positive: Pathogenic Variant(s) Identified

DISEASE INFO	PATIENT RESULT	PARTNER RESULT
3-Methylcrotonyl-CoA Carboxylase Deficiency **Gene:** MCCC2 **Inheritance Pattern:** Autosomal Recessive	**Variant:** c.295G>C (p.Glu99Gln) **Zygosity:** Heterozygous **Pathogenicity:** Likely Pathogenic	**No pathogenic variant(s) identified.**
Alpha-1-Antitrypsin Deficiency **Gene:** SERPINA1 **Inheritance Pattern:** Autosomal Recessive	**Variant:** c.863A>T (p.Glu288Val) **Zygosity:** Heterozygous **Pathogenicity:** Observed Pathogenic	**No pathogenic variant(s) identified.**
Stargardt Disease **Gene:** ABCA4 **Inheritance Pattern:** Autosomal Recessive	**Variant:** c.3113C>T (p.Ala1038Val) **Zygosity:** Heterozygous **Pathogenicity:** Observed Pathogenic	**No pathogenic variant(s) identified.**
Muscular Dystrophies **Gene:** DMD **Inheritance Pattern:** X-Linked	**No pathogenic variant(s) identified.**	**Variant:** Exon 52/79 DEL **Zygosity:** Heterozygous **Pathogenicity:** Likely Pathogenic
Fragile X Syndrome **Gene:** FMR1 **Inheritance Pattern:** X-Linked	**CGG Repeat 1:** 31 Repeats (Wildtype) **CGG Repeat 2:** 31 Repeats (Wildtype) **No pathogenic variant(s) identified.**	**CGG Repeat 1:** 55 Repeats (Pre-Mutation) **CGG Repeat 2:** 32 Repeats (Wildtype) **Pathogenicities:** Observed Pathogenic

INTERPRETATION

The patient is Heterozygous for a Substitution (MCCC2: c.295G>C (p.Glu99Gln)) on chromosome 5. This result indicates that this patient may be affected with, or predisposed to developing, 3-Methylcrotonyl-CoA Carboxylase Deficiency The patient is Heterozygous for a Substitution (ABCA4: c.3113C>T (p.Ala1038Val)) on chromosome 1. This result indicates that this patient may be affected with, or predisposed to developing, Stargardt Disease. The patient is Heterozygous for a Substitution (SERPINA1: c.863A>T (p.Glu288Val)) on chromosome 14. This result indicates that this patient may be affected with, or predisposed to developing, Alpha-1-Antitrypsin Deficiency. The patient is Heterozygous for a Substitution (MCCC2: c.295G>C (p.Glu99Gln)) on chromosome 5. This result indicates that this patient may be affected with, or predisposed to developing, 3-Methylcrotonyl-CoA Carboxylase Deficiency.

Medical management for this patient should be based on clinical and family history. Only the genes, and regions thereof, that are listed in this report were tested. Genetic changes in regions/genes not analyzed could contribute to a patient's phenotype.

RECOMMENDATION

Clinical follow-up is recommended for appropriate management. Genetic counseling is recommended for this patient.

3-Methylcrotonyl-CoA Carboxylase Deficiency

Description

In this disease, patients are deficient in an enzyme (3-Methylcrotonyl-CoA Carboxylase) that breaks down proteins containing a particular amino acid called leucine. In the MCCA related form of this disease, the gene that creates the alpha subunit of the enzyme is defective. As a result, proteins containing leucine are not properly processed in the body and accumulate as byproducts toxic in the brain. Infants with this disease appear normal at birth but develop symptoms that range from mild to life-threatening during infancy and early childhood. Characteristic symptoms include feeding difficulties, recurrent episodes of vomiting and diarrhea, excessive tiredness, and weak muscle tone.

Prognosis

Prognosis is highly variable. While some patients present with severe neurological abnormalities and death in infancy, more than 90% of patients are asymptomatic through adulthood. However, outcome is enhanced by diagnosis in the first 10 days of life.

Treatment

Treatment includes a diet low in proteins and use of compounds that either dispose of toxic byproducts of improper protein processing or that boost the activity of the deficienct enzyme.

Statistics

This disease is more common in North America, Europe, and Australia. The overall frequency of MCC deficiency, including MCCA and MCCB related, is approximately 1 in 50,000. Studies have found that MCCA mutations may account for approximately 35% of MCC deficiency. Based on this, MCCA related MCC deficiency has a calculated incidence of 1 in 140,000.

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Alpha-1-Antitrypsin Deficiency

Description

Alpha-1 Antitrypsin Deficiency is an inherited condition that can cause lung and liver disease. This disease is caused by mutations in the SERPINA1 gene, which is normally responsible for producing alpha-1 antitrypsin protein. This protein controls the activity of the neutrophil elastase enzyme, which is released by white blood cells to fight infection. Without adequate alpha-1 antitrypsin, neutrophil elastase can damage healthy lung tissue. Abnormally formed alpha-1 antitrypsin can also accumulate in the liver, where it is produced, and damage liver tissue. Affected individuals develop lung disease between the ages of 20 and 50. The most common symptom is emphysema, a chronic condition caused by damage to the air sacs in the lungs that leads to coughing, difficulty breathing, and limits physical activity. A smaller proportion of affected patients also develop liver disease as children or as adults, leading to jaundice and sometimes liver failure.

Prognosis

Prognosis is generally favorable. Non-smokers often have a normal life span. Smoking, however, greatly accelerates the disease, particularly as it affects the lungs. Onset of lung disease typically occurs in adulthood. Liver disease presents in only 2% of affected children. Liver disease, however, affects about 19% of adults who live past 50 with this disease.

Treatment

Lung transplantation or liver transplantation may be appropriate for patients with end-stage lung disease or liver disease due to Alpha-1-Antitrypsin Deficiency. In general, patients should avoid smoking. Vitamin E therapy has been demonstrated to improve liver function in symptomatic infants and may help prevent oxidative damage to the lungs.

Statistics

This disease is one of the most common metabolic disorders in the Caucasian and Hispanic populations in the U.S., but is present in lower frequencies in Asian and African populations. In the U.S. the disease affects 1 in 5,000 newborns. Worldwide, this disease has higher incidence among European populations, particularly in Scandinavian countries.

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Stargardt Disease

Description

Stargardt disease is a genetic eye disorder that causes progressive vision loss or macular degeneration. The disorder is caused by mutations in the ABCA4 gene, which normally provides instructions for making proteins that are found in light-sensing (photoreceptor) cells in the retina. Stargardt disease is one of the most frequent causes of macular degeneration in childhood; its onset occurs between 6 and 12 years of age. Visual acuity is severely reduced but peripheral visual fields remain normal throughout life. By 20 years of age, symptoms include wavy vision, blind spots, blurriness, impaired color vision, and difficulty adapting to dim lighting.

Prognosis

The long term prognosis for patients with Stargardt disease is widely variable. General health is not affected and some affected individuals are still able to drive.

Treatment

No specific treatments are available for Stargardt disease. Many affected individuals use magnifiers for visual assistance and wear sunglasses to slow the development of the condition.

Statistics

The estimated incidence of Stargardt disease is 1 in 10,000 individuals.

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Muscular Dystrophies

Description

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are caused by mutations in the DMD gene, responsible for producing the dystrophin protein. These genetic conditions are characterized by progressive muscle weakness and wasting, or atrophy. DMD and BMD primarily affect the skeletal muscles and cardiac muscles. The signs and symptoms of each condition are very similar; the disorders differ mostly in their severity, age of onset, and rate of progression. Individuals affected with DMD develop muscle weakness in early childhood that worsens rapidly. They are usually wheelchair-dependent by adolescence. Individuals with DMD also develop cardiomyopathy, a form of heart disease that weakens the cardiac muscle and prevents the heart from pumping blood efficiently. Affected males typically die from complications in their twenties. Individuals with BMD develop muscle weakness later in childhood or in adolescence, which worsens at a much slower rate than is seen in DMD. Individuals with BMD are also likely to develop cardiomyopathy. In some cases, individuals with mutations in the DMD gene will primarily develop cardiomyopathy without general muscular dystrophy. Furthermore, female carriers of DMD mutations are at increased risk for cardiomyopathy.

Prognosis

Prognosis is generally unfavorable. Those affected with DMD are diagnosed at an average age of 5 years and become wheelchair dependent around 10 years. Cardiac muscle failure develops in 15% of affected individuals at a median age of 21 years. In general, however, death occurs around 17 years of age. Prognosis for those affected with BMD is slightly more favorable with individuals remaining ambulatory into their 20s and not requiring a wheelchair until after they are 16 years old. Cardiac muscle involvement is significant, however, with mean age of cardiomyopathy diagnosis at 15 years and mean age of death in the mid-40s.

Treatment

Treatment includes corticosteroids to improve the strength and muscle function in affected individuals. Physical therapy is also recommended to promote mobility and prevent contractures. Cardiomyopathy is treated with ACE inhibitors, beta blockers, and, if necessary, cardiac transplants.

Statistics

This X-linked disease affects males and very rarely affects females. DMD/BMD is estimated to affect 1 in 3,500 - 5,000 newborn males. In the United States, approximately 500 males are born with these conditions each year.

References

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Fragile X Syndrome

Description

Fragile X syndrome is an X-linked condition associated with learning disabilities and cognitive impairment. This condition is caused by mutations in the FMR1 gene, which is responsible for neural development. Affected individuals exhibit intellectual disability and may develop behavioral abnormalities including autism spectrum disorders, attention deficit disorder, and anxiety disorders. Affected males often present with characteristic physical features including long narrow face, large ears, a prominent jaw and forehead, flexible fingers, and enlarged testicles following puberty. Affected females may have milder symptoms. As the condition is X-linked, it is more common in males than in females.

Prognosis

Prognosis is variable. Affected males typically demonstrate developmental delay and may have autism spectrum disorders. Affected females display a wider spectrum of features, but may have significant intellectual involvement and autism spectrum disorder as well. Affected individuals typically do not have a shortened lifespan.

Treatment

Treatment is primarily supportive. Early intervention and special education classes are indicated. Medication may be indicated for behavioral issues on a case-by-case basis.

Statistics

Fragile X syndrome is a relatively common condition. It is estimated to affect approximately 1 in 5,000 males and 1 in 10,000 females in the general population. One large scale study found that approximately 1 in 100 women in the general population is a carrier for this condition.

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GENES ASSAYED

ABCA12 (NM_173076)	ABCA4 (NG_009073)	ABCB11 (NM_003742)	ABCC8 (NM_000352)	ABCD1 (NM_000033)
ACADM (NM_000016)	ACADS (NM_000017)	ACADVL (NM_000018)	ACAT1 (NM_000019)	ACOX1 (NM_004035)
ADA (NM_000022_)	ADAMTS2 (NM_014244)	AGA (NM_000027)	AGL (NM_000642)	AGXT (NM_000030)
AIRE (NM_000383)	ALDH3A2 (NM_001031806)	ALDOB (NM_000035)	ALG6 (NM_013339)	ALPL (NM_000478)
AMH (NM_000479)	AMHR2 (NM_020547)	AMT (NM_000481)	AR (NM_000044)	ARG1 (NM_000045)
ARSA (NM_000487)	ARSB (NM_000046)	ASL (NM_001024943)	ASNS (NM_001673)	ASPA (NM_000049)
ASS1 (NM_000050)	ATM (NM_000051)	ATP6V1B1 (NM_001692)	ATP7A (NG_013224)	ATP7B (NM_000053)
BBS1 (NM_024649)	BBS10 (NM_024685)	BBS12 (NM_152618)	BBS2 (NM_031885)	BCHE (NM_000055)
BCKDHA (NM_000709)	BCKDHB (NM_183050)	BCS1L (NM_004328)	BLM (NM_000057)	BRIP1 (NM_032043)
BSND (NM_057176)	BTD (NM_000060)	CAPN3 (NG_008660)	CBS (NM_000071)	CDH23 (NM_022124)
CEP290 (NG_008417)	CERKL (NM_201548)	CFTR (NM_000492)	CHM (NM_000390)	CHRNE (NM_000080)
CHRNG (NM_005199)	CHRX (NC_000023)	CHRY (NC_000024)	CIITA (NM_000246)	CLN5 (NM_006493)
CLN6 (NM_017882)	CLN8 (NM_018941)	CLRN1 (NM_174878)	COL4A3 (NM_031362)	COL4A4 (NM_000092)
COL4A5 (NM_000495)	COL7A1 (NM_000094)	CPT1A (NM_001876)	CPT2 (NM_000098)	CTNS (NM_001031681)
CTSC (NM_001814)	CTSK (NM_000396)	CYBA (NM_000101)	CYBB (NM_000397)	CYP11B1 (NG_007954)
CYP11B2 (NM_000498)	CYP17A1 (NM_000102)	CYP19A1 (NM_031226)	CYP1B1 (NM_000104)	CYP21A2 (NM_000500)
CYP27A1 (NM_000784)	DBT (NM_001918)	DCLRE1C (NG_007276)	DHCR7 (NM_001360)	DHDDS (NM_205861)
DLD (NM_000108)	DMD (NM_004006)	DNAI1 (NM_012144)	DNAI2 (NM_023036)	DOK7 (NM_173660)
DYSF (NG_008694)	EDA (NM_001399)	EIF2AK3 (NM_004836)	EIF2B5 (NM_003907)	EMD (NM_000117)
ERCC6 (NM_000124)	ERCC8 (NM_000082)	ETFA (NM_000126)	ETFB (NM_001014763)	ETFDH (NM_004453)
ETHE1 (NM_014297)	EVC (NM_153717)	EVC2 (NM_147127)	EXOSC3 (NM_016042)	F8 (NM_000132)
F9 (NM_000133)	FAH (NM_000137)	FAM161A (NM_001201543)	FANCA (NG_011706)	FANCC (NM_000136)
FANCG (NG_007312)	FH (NM_000143)	FKRP (NM_001039885)	FKTN (NM_001198963)	FMR1 (NM_002024)
G6PC (NM_000151)	G6PD (NM_000402)	GAA (NM_000152)	GALC (NM_000153)	GALK1 (NM_000154)
GALNS (NM_000512)	GALT (NM_000155)	GAMT (NM_000156_)	GBA (NM_000157)	GBE1 (NM_000158)
GCDH (NM_000159)	GDF5 (NM_000557)	GJB1 (NM_001097642)	GJB2 (NM_004004)	GLA (NM_000169)
GLB1 (NM_000404)	GLDC (NM_000170_)	GNE (NM_001128227)	GNPTAB (NM_024312)	GNS (NG_008955)
GRHPR (NM_012203)	GUCY2D (NG_009092)	GUSB (NM_000181)	HADHA (NM_000182)	HADHB (NM_000183)
HAX1 (NM_006118)	HBA1 (NM_000558)	HBA2 (NM_000517)	HBB (NM_000518)	HEXA (NM_000520)
HEXB (NM_000521)	HFE2 (NM_213653)	HGD (NM_000187)	HGSNAT (NG_009552)	HLCS (NM_000411)
HMGCL (NM_000191)	HOGA1 (NM_138413)	HPS1 (NG_009646)	HPS3 (NM_032383)	HPS4 (NM_152841)
HSD17B3 (NM_000197)	HSD17B4 (NM_000414)	HSD3B2 (NM_000198)	IDS (NM_000202)	IDUA (NM_000203)
IKBKAP (NM_003640)	IL2RG (NM_000206)	IVD (NM_002225)	KCNJ11 (NM_000525)	LAMA3 (NM_198129)
LAMB3 (NM_000228)	LAMC2 (NM_005562)	LCA5 (NM_181714)	LHCGR (NM_000233)	LIFR (NM_002310)
LIPA (NM_000235)	LOXHD1 (NM_144612)	LPL (NM_000237)	LRPPRC (NM_133259)	LYST (NM_000081)
MAN2B1 (NM_000528_)	MCCC1 (NM_020166)	MCCC2 (NM_022132)	MCOLN1 (NM_020533)	MED17 (NM_004268)

MEFV (NM_000243)
MFSD8 (NM_152778)
MKS1 (NG_013032)
MLC1 (NG_009162)
MLYCD (NM_012213)
MMAA (NM_172250_)
MMAB (NM_052845_)
MMACHC (NM_015506)
MPI (NM_002435)
MPL (NM_005373)
MPV17 (NG_008075)
MTHFR (NM_005957)
MTM1 (NM_000252)
MTTP (NM_000253)
MUT (NM_000255_)
MYO15A (NM_016239)
MYO7A (NM_000260)
NAGLU (NG_011552)
NBN (NM_002485)
NDUFS6 (NM_004553)
NEB (NM_001164508)
NPC1 (NM_000271)
NPC2 (NM_006432)
NPHS1 (NM_004646)
NPHS2 (NM_014625)
NR2E3 (NM_016346)
NTRK1 (NM_002529)
OCRL (NM_000276)
OPA3 (NM_025136_)
OTC (NM_000531)
PAH (NM_000277)
PC (NM_022172)
PCCA (NM_000282_)
PCCB (NM_000532_)
PCDH15 (NM_033056)
PDHA1 (NM_000284)
PDHB (NM_000925)
PEX1 (NM_000466)
PEX10 (NM_153818)
PEX2 (NG_008371)
PEX6 (NG_008370)
PEX7 (NM_000288)
PFKM (NM_000289)
PHGDH (NG_009188)
PKHD1 (NM_138694)
PMM2 (NM_000303)
POLG (NG_008218)
POMGNT1 (NM_017739)
POR (NG_008930)
PPT1 (NM_000310)
PROP1 (NM_006261)
PRPS1 (NM_002764)
PTS (NM_000317)
PUS1 (NM_025215)
PYGM (NM_005609)
RAB23 (NG_012170)
RAG2 (NM_000536)
RAPSN (NM_005055)
RARS2 (NM_020320)
RDH12 (NG_008321)
RLBP1 (NG_008116)
RMRP (NR_003051)
RPE65 (NM_000329)
RS1 (NM_000330)
RTEL1 (NG_033901)
SACS (NM_014363)
SEPSECS (NM_016955)
SERPINA1 (NM_001002236)
SGCA (NM_000023)
SGCB (NM_000232)
SGCD (NG_008693)
SGCG (NG_008759)
SGSH (NG_008229)
SLC12A3 (NM_001126107)
SLC12A6 (NM_133647)
SLC17A5 (NM_012434)
SLC22A5 (NM_003060)
SLC25A13 (NM_001160210)
SLC25A15 (NM_014252)
SLC25A20 (NM_000387)
SLC26A2 (NM_000112)
SLC26A3 (NM_000111)
SLC26A4 (NM_000441)
SLC35A3 (NG_033857)
SLC37A4 (NM_001164277)
SLC39A4 (NM_130849)
SLC3A1 (NG_008233)
SLC45A2 (NG_011691)
SLC4A11 (NM_032034)
SLC7A7 (NG_012851)
SLC7A9 (NM_001243036)
SMN1 (NM_022874)
SMPD1 (NM_000543)
SRD5A2 (NG_008365)
STAR (NM_000349)
SUMF1 (NG_016225)
TAT (NM_000353)
TCIRG1 (NM_006019)
TECPR2 (NM_014844)
TFR2 (NM_003227)
TGM1 (NG_007150)
TH (NM_199292)
TMEM216 (NM_016499)
TPP1 (NM_000391)
TRIM32 ()
TRMU (NM_018006)
TSEN54 (NM_207346)
TTC37 (NM_014639)
TTPA (NM_000370)
TYMP (NM_001257989)
TYR (NG_008748)
TYRP1 (NM_000550)
UGT1A1 (NM_000463)
USH1C (NM_005709)
USH2A (NM_206933_)
VPS13A (NM_015186)
VPS13B (NG_007098)
VPS53 (NG_034190)
VRK1 (NM_003384)
VSX2 (NM_182894)
WAS (NM_000377)
WRN (NG_008870)
XPA (NM_000380)
XPC (NM_004628)

METHODS & LIMITATIONS

SEQUENCING

Sequencing is performed using a custom next-generation sequencing platform. Only the specified regions of genes are assayed via next-generation sequencing. This methodology may not detect low-level mosaicism. Exons containing only untranslated regions are not assayed. 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 mutations in those regions may not be reliably identified. All mutations included within the genes assayed may not be detected. All clinically significant observations are confirmed by orthogonal techniques as part of our ongoing quality managment process.

LIMITATIONS

This test is designed to detect specific mutations associated with monogenic recessive and x-linked genetic disease for the purpose of assessing parental carrier status. It cannot detect every mutation associated with these diseases, nor does it look for all known genetic diseases. Therefore, a negative result on this test is risk reducing but not risk eliminating. Although this test is highly accurate, no genetic test is 100% accurate. Novel sequence changes in the promoter region and other non-coding regions will not be detected by this assay. This methodology may not detect low-level mosaicism. Exons containing only untranslated regions are not assayed. 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 mutations in those regions may not be reliably identified. All mutations included within the genes assayed may not be detected.

For some genes, only specific variants are assayed. The possibility that other variants within these genes contribute to disease cannot be excluded. As new informa-tion becomes available, variant classification may evolve over time. Providers are encouraged to contact support@phosphorus.com to obtain updated information.

This report does not constitute medical advice. Any questions or concerns regarding the contents of this report should be directed to a qualified medical geneticist, genetic counselor, or reproductive endocrinologist. This report reflects the analysis of an extracted DNA sample. In very rare cases, the analyzed DNA may not represent that patient's constitutional genome. Examples include but are not limited to: circulating hematolymphoid neoplasm, bone marrow transplantation, blood transfusion, sample contamination, sample mix-up, and technical errors.

This test was developed and its performance determined by Phosphorus, Inc., and has not been approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such approval is not necessary.

Routine cytogenetic analysis may not detect low-level mosaicism, microdeletions, single gene mutations or other subtle structural rearrangements.

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 physician 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 or likely pathogenic are reported. Variants determined to be of uncertain significance, likely benign or benign are not reported, but are available upon request. Variants are classified in accordance with ACMG guidelines (PMID: 25741868).

SIGNED BY

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