PHOENIX MED LAB

Phoenix Med Lab
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PATIENT INFORMATION

Patient Name:

Age: 61
Sex: Female
Ethnicity:

PROVIDER INFORMATION

Physician: xxxxxxxxxxxxxxxx
Client: xxxxxxxxxxxxxx
Client ID:

SPECIMEN

Accession ID: 1907083025
Specimen Type: Buccal Swab
Collection Date: Jul 4, 2019
Date Accessioned: Jul 8, 2019
Date Reported: Jul 23, 2019

TEST PERFORMED

C-55 (Comprehensive Panel)

Targeted next-generation sequencing was performed on this specimen. See Methods and Limitations section for more information.

RESULT

Variant of Unknown Significance Detected

Uncertain – A variant of uncertain significance (VUS) was detected in this report. This indicates a genetic change for which there is no reliable data or knowledge at this time to indicate if the detected change is linked to an increased cancer risk or not. These test result indicate you have at least the same risk of cancer as the general population. However, your risk could be increased relative to the general population if you carry variants this assay does not test for. Alternatively, the VUS variant(s) identified here may be associated with disease in the future, indicating an increased risk of cancer. Your physician will discuss the results with you and what they mean and may recommend you discuss your results with a genetic counselor.

VARIANT SUMMARY

Variants Detected	Genotype	Phenotype	Assessment
CDKN1C c.*6-14C>A -	Heterozygous	Beckwith-wiedemann Syndrome	**Uncertain Significance**

VARIANT INTERPRETATION

CDKN1C c.*6-14C>A - **Uncertain Significance**	**Interpretation:** The gene CDKN1C codes for the cyclin dependent kinase inhibitor 1C protein. This protein acts as a tumor suppressor, which means that it keeps cells from growing and dividing too fast or in an uncontrolled way. Pathogenic variants in the CDKN1C gene lead to Beckwith-Wiedemann syndrome (BWS), a disorder characterized by anterior abdominal wall defects including exomphalos (omphalocele), pre- and postnatal overgrowth, and macroglossia [4, PMID:26077438; OMIM:130650]. In about 85 percent of BWS cases, only one person in a family has been diagnosed with the condition. In most families, the condition appears to have an autosomal dominant pattern of inheritance. Children with BWS are at an increased risk of developing several types of cancerous and noncancerous tumors, particularly a form of kidney cancer called Wilms tumor and a form of liver cancer called hepatoblastoma. [6, 6, 3]. BWS has an estimated 1 in 13,700 birth incidence. Pathogenic variants in the CDKN1C gene have also been found to cause intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies, commonly known by the acronym IMAGe [2, 1, 5, 3; OMIM:614732].

GENES TESTED

APC, ATM, AXIN1, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDKN1C, CDKN2A, CHEK2, DICER1, DIS3L2, EPCAM, FH, FLCN, GPC3, GREM1, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PAKAR1A, PALB2, PMS2, POLD1, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RB1, REQL4, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, SMARC4A, STK11, SUFU, TP53, TSC1, TSC2, VHL, WT1

METHODS AND LIMITATIONS

DNA extracted from patient's saliva sample is quantified using Qubit 2.0 Fluorimeter (Life Technologies Inc.). **Germline mutations of *APC, ATM, AXIN1, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDKN1C, CDKN2A, CHEK2, DICER1, DIS3L2, EPCAM, FH, FLCN, GPC3, GREM1, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PAKAR1A, PALB2, PMS2, POLD1, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RB1, REQL4, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, SMARC4A, STK11, SUFU, TP53, TSC1, TSC2, VHL, WT1* genes are tested by sequencing the entire coding region for each gene with 5 bp of padding at both ends.** The panel consists of amplicons that cover 98% of all coding regions of the genes listed above. Each sample template is tagged with a unique barcode for sample identification before processing. Sequencing is performed on the Ion Torrent S5 (Life Technologies Inc.) using AmpliSeq and Ion Chef technologies, and Hi-Q View chemistry. Data obtained are analyzed using the Applied Biosystems Ion Torrent variant analyzing software, which includes signal processing, base calling,quality score assignment, adapter trimming, alignment to human genome 19 reference (hg19), coverage analysis, and variant calling. Variant annotation is performed on the QIAGEN Clinical Insight software. **Sanger sequencing confirmation is performed on all pathogenic, likely pathogenic, and variant of unknown significance samples through Eurofins Clinical Molecular Testing Services, LLC.**

Based on validation studies, our method has a >95% sensitivity and specificity for detecting single nucleotide variants, insertions/deletions, and other frame shift mutations. However, some rare and novel genetic variations might not be detected by this method. Genes other then those listed above that are associated with certain types of cancer are beyond the scope of this test.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (5.5.20190701), Ingenuity Knowledge Base (Utopia 190618.002), CADD (v1.4), Allele Frequency Community (2018-12-15), EVS (ESP6500SI-V2), Refseq Gene Model (2018-07-10), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2019-06-18 17:54:05.0), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (Utopia 190618.002), PolyPhen-2 (v2.2.2), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Jun 28 11:10 iva-1.0.1085.jar), PhyloP hg18 (2009-11), PhyloP hg19 (2009-11), DbSNP (151), TargetScan (7.2), GENCODE (Release 28), CentoMD (5.3), OMIM (May 26, 2017), gnomAD (2.0.1), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2019-01-02), DGV (2016-05-15), COSMIC (v87), HGMD (2018.4), SIFT4G (2016-02-23)

DISCLAIMER

False positives and false negatives are possible. Such errors can be due to contamination, technical errors, and interference from rare genetic variants. It is recommended to consider alternative methods before taking any clinical action. Consulting your results with a genetic counselor is highly recommended. This test was developed, and its performance characteristics determined by Capstone Diagnostics. The US Food and Drug Administration does NOT require this test to go through pre-market Food and Drug Administration (FDA) review. The laboratory is regulated and accredited by CLIA and the Joint Commission (JCHO) as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.

SELECTED CITATIONS

1. Arboleda VA, Lee H, Parnaik R, Fleming A, Banerjee A, Ferraz-de-Souza B, Délot EC, Rodriguez-Fernandez IA, Braslavsky D, Bergadá I, Dell'Angelica EC, Nelson SF, Martinez-Agosto JA, Achermann JC, Vilain E (2012) Mutations in the PCNA-binding domain of CDKN1C cause IMAGe syndrome. Nat Genet. 2012 May 27;44(7):788-92 (PMID: 22634751)

2. Bergadá I, Del Rey G, Lapunzina P, Bergadá C, Fellous M, Copelli S (2005) Familial occurrence of the IMAGe association: additional clinical variants and a proposed mode of inheritance. J Clin Endocrinol Metab. 2005 Jun;90(6):3186-90. Epub 2005 Mar 15 (PMID: 15769992)

3. Eggermann T, Algar E, Lapunzina P, Mackay D, Maher ER, Mannens M, Netchine I, Prawitt D, Riccio A, Temple IK, Weksberg R (2013) Clinical utility gene card for: Beckwith-Wiedemann Syndrome. Eur J Hum Genet. 2014 Mar;22(3). Epub 2013 Jul 3 (PMID: 23820480)

4. Lam WW, Hatada I, Ohishi S, Mukai T, Joyce JA, Cole TR, Donnai D, Reik W, Schofield PN, Maher ER (1999) Analysis of germline CDKN1C (p57KIP2) mutations in familial and sporadic Beckwith-Wiedemann syndrome (BWS) provides a novel genotype-phenotype correlation. J Med Genet. 1999 Jul;36(7):518-23 (PMID: 10424811)

5. Pedreira CC, Savarirayan R, Zacharin MR (2004) IMAGe syndrome: a complex disorder affecting growth, adrenal and gonadal function, and skeletal development. J Pediatr. 2004 Feb;144(2):274-7 (PMID: 14760276)

6. Rump P, Zeegers MP, van Essen AJ (2005) Tumor risk in Beckwith-Wiedemann syndrome: A review and meta-analysis. Am J Med Genet A. 2005 Jul 01;136(1):95-104 (PMID: 15887271)

Reviewed and approved by: xxxxxxxxx, Laboratory Director

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