Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: TEST,

Patient: POS, PGLPCC

DOB
Sex: Female
Patient Identifiers: 46688
Visit Number (FIN): 47017
Collection Date: 2/21/2023 14:20

Hereditary Paraganglioma-Pheochromocytoma Expanded Panel, Sequencing and Deletion/Duplication

ARUP test code 3005912

Spcm PGLPCC	Whole Blood
PGLPCC Interp	Positive

RESULT
One pathogenic variant was detected in the SDHB gene.

PATHOGENIC VARIANT
Gene: SDHB (NM_003000.2)
Nucleic Acid Change: c.286+1G>A; Heterozygous
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.286+1G>A, was detected in the SDHB gene by massively parallel sequencing. This result is consistent with a diagnosis of hereditary paraganglioma/pheochromocytoma syndrome; clinical manifestations are variable. This individuals offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The SDHB c.286+1G>A variant (rs786201063), also known as IVS3+1G>A, is reported in the literature in multiple individuals affected with paragangliomas and pheochromocytomas (Brouwers, 2006; Isobe, 2007; Pandit, 2016; Timmers, 2007). This variant is reported in ClinVar (Variation ID: 183757). This variant is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant disrupts the canonical splice donor site of intron three, which is likely to negatively impact gene function. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic SDHB variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

H=High, L=Low, *=Abnormal, C=Critical

REFERENCES
Brouwers FM, et al. High frequency of SDHB germline mutations in patients with malignant catecholamine-producing paragangliomas: implications for genetic testing. J Clin Endocrinol Metab. 2006;91(11):4505-9. PMID: 16912137.

Isobe K, et al. Novel germline mutations in the SDHB and SDHD genes in Japanese pheochromocytomas. Horm Res. 2007;68(2):68-71. PMID: 17308434.

Pandit R, et al. Germline mutations and genotype-phenotype correlation in Asian Indian patients with pheochromocytoma and paraganglioma. Eur J Endocrinol. 2016;175(4):311-23. PMID: 27539324.

Timmers HJ, et al. Clinical presentations, biochemical phenotypes, and genotype-phenotype correlations in patients with succinate dehydrogenase subunit B-associated pheochromocytomas and paragangliomas. J Clin Endocrinol Metab. 2007;92(3):779-86. PMID: 17200167.

BACKGROUND INFORMATION: Hereditary Paraganglioma-Pheochromocytoma Expanded Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes. PGL/PCC syndromes are characterized by the presence of paragangliomas (neuroendocrine tissue derived tumors) and pheochromocytomas (paragangliomas confined to the adrenal medulla). Hereditary PGL/PCC is often characterized by early disease onset and the presence of multiple (or recurrent) paragangliomas/pheochromocytomas and a family history.

EPIDEMIOLOGY: It is estimated that hereditary disease accounts for approximately 35-40% of PGL/PCC.

CAUSE: Pathogenic germline variants in genes associated with high lifetime risk of paraganglioma and/or pheochromocytoma

INHERITANCE: Autosomal dominant; some genes may show a parent-of-origin effect.

GENES TESTED: FH; MAX; MEN1*; NF1; RET; SDHA*; SDHAF2; SDHB; SDHC*; SDHD*; TMEM127; VHL*

*One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis. Deletion/duplication testing of the SDHB, SDHC, and SDHD genes was performed by multiplex ligation-dependent probe amplification (MLPA).

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs

in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes. The analytical sensitivity for MLPA is greater than 99 percent.

LIMITATIONS: A negative result does not exclude a heritable form of paraganglioma/pheochromocytoma or other cancer. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes.
Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
MEN1 (NM_001370251) exon 8
SDHA (NM_004168) exon 14
SDHA (NM_001294332) exon 13
SDHA (NM_001330758) exon 12
SDHC (NM_001035511) partial exon 5 (Chr1:161332225-161332330)
SDHC (NM_001278172) partial exon 4 (Chr1:161332225-161332330)
SDHD (NM_001276506) exon 4
VHL (NM_001354723) exon 2

Deletions/duplications will not be called for the following exons:
MEN1 (NM_001370251) 8; SDHA (NM_004168) 1,10-15; SDHA (NM_001294332) 1,9-14; SDHA (NM_001330758) 1,10-13; VHL (NM_001354723) 2

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Spcm PGLPCC	23-052-116737	2/21/2023 2:20:00 PM	2/21/2023 2:20:34 PM	2/21/2023 2:23:00 PM

H=High, L=Low, *=Abnormal, C=Critical

PGLPCC Interp	23-052-116737	2/21/2023 2:20:00 PM	2/21/2023 2:20:34 PM	2/21/2023 2:23:00 PM

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical