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Client: Example Client ABC123
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Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/10/1967
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hereditary Paraganglioma-Pheochromocytoma (SDHA, SDHB, SDHC, and SDHD) Sequencing and Deletion/Duplication

ARUP test code 3004480

SDH Specimen	Whole Blood

SDH Interp

Positive

RESULT
One pathogenic variant was detected in the SDHB gene.

PATHOGENIC VARIANT
Gene: SDHB (NM_003000.3)
Nucleic Acid Change: c.418G>T; Heterozygous
Amino Acid Alteration: p.Val140Phe
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.418G>T; p.Val140Phe, was detected in the SDHB gene by massively parallel sequencing. This result is consistent with a diagnosis of Hereditary Paraganglioma-Pheochromocytoma Syndrome type 4 (PGL4), which is associated with a high risk for malignancy; clinical manifestations are variable. National Comprehensive Cancer Network (NCCN) guidelines are available for cancer risk management. Other genetic/environmental factors may influence an individual's risk of developing cancer. This individual's offspring have a 50 percent risk 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.418G>T; p.Val140Phe variant (rs267607032) is reported in the literature in multiple individuals with paragangliomas (Brouwers 2006, Niemeijer 2017, Prodanov 2009, Santiago 2010, Schimke 2010, Timmers 2008) and was shown to segregate with disease in at least two families (Santiago 2010, Schimke 2010). This variant is also reported in ClinVar (Variation ID: 18454) and is only observed on 3 alleles in the Genome Aggregation Database, indicating it is not a common polymorphism. Computational analyses predict that this variant is deleterious (REVEL: 0.857). 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).

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

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

REFERENCES
National Comprehensive Cancer Network. Neuroendocrine and Adrenal Tumors. (1.2023): https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

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 Nov;91(11):4505-9. PMID: 16912137.

Niemeijer ND et al. The phenotype of SDHB germline mutation carriers: a nationwide study. Eur J Endocrinol. 2017 Aug;177(2):115-125. PMID: 28490599

Prodanov T et al. Malignant paraganglioma associated with succinate dehydrogenase subunit B in an 8-year-old child: the age of first screening? Pediatr Nephrol. 2009 Jun;24(6):1239-42. PMID: 19189136.

Santiago AH et al. Early presentation of familial paraganglioma with SDHB mutation in a 13 year old child and its mother. J Pediatr Endocrinol Metab. 2010 Apr;23(4):419-22. PMID: 20583550

Schimke RN et al. Paraganglioma, neuroblastoma, and a SDHB mutation: Resolution of a 30-year-old mystery. Am J Med Genet A. 2010 Jun;152A(6):1531-5. PMID: 20503330

Timmers HJ et al. Biochemically silent abdominal paragangliomas in patients with mutations in the succinate dehydrogenase subunit B gene. J Clin Endocrinol Metab. 2008 Dec;93(12):4826-32. PMID: 18840642

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Hereditary Paraganglioma-Pheochromocytoma (SDHA, SDHB, SDHC, and SDHD) Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are familial cancer syndromes characterized by neuroendocrine tumors: paragangliomas (neuroendocrine tumors of the autonomic nervous system) and pheochromocytomas (paragangliomas of the adrenal medulla). Pathogenic germline variants in SDHA, SDHB, SDHC, and SDHD, among several other genes, predispose individuals to paraganglioma and pheochromocytoma with an increased risk for malignancy.

CAUSE: Pathogenic germline variants in succinate dehydrogenase, subunits A, B, C, and D (SDHA, SDHB, SDHC, and SDHD), and other genes

INHERITANCE: Autosomal dominant; parent-of-origin effect for SDHD

PENETRANCE: Variable and age dependent

CLINICAL SENSITIVITY: 22-45 percent

GENES TESTED: SDHA* (NM_004168), SDHB (NM_003000), SDHC (NM_003001), SDHD (NM_003002)
* - One or more exons are not covered by sequencing, and

deletion/duplication detection is not available for this 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. Human genome build 19 (Hg 19) was used for data analysis. Multiplex ligation-dependent probe amplification (MLPA) of the targeted genes.

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. 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 diagnosis of hereditary paraganglioma-pheochromocytoma. This test only detects variants within the coding regions and intron-exon boundaries of the SDHA, SDHB, SDHC, and SDHD 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. 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) mutations, 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:
SDHA(NM_004168) exon 14

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
SDH Specimen	23-258-401241	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
SDH Interp	23-258-401241	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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