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

Physician: arup, arup

Patient: Genomics, SDH NGS 1

DOB	
Sex:	Female
Patient Identifiers:	36455
Visit Number (FIN):	36774
Collection Date:	2/23/2022 12:00

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 SDHD gene.

PATHOGENIC VARIANT
Gene: SDHD (NM_003002.4)
Nucleic Acid Change: c.242C>T; heterozygous
Amino Acid Alteration: p.Pro81Leu
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.242C>T; p.Pro81Leu, was detected in the SDHD gene by massively parallel sequencing. This result is consistent with a diagnosis of hereditary paraganglioma-pheochromocytoma syndrome type 1 (PGL1). Disease manifestations are variable. This individual's offspring have a 50 percent risk of inheriting the causative pathogenic variant; however, disease manifestation generally only occurs when pathogenic variants in SDHD are inherited paternally, due to a parent-of-origin effect. 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.

No additional pathogenic variants were identified in the SDHA, SDHB, SDHC, or SDHD genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for limitations of this test.

Evidence for variant classification:
The SDHD c.242C>T; p.Pro81Leu variant (rs80338844) has been reported in several familial and sporadic cases of paraganglioma (PGL) (Baysal, 2000; Baysal, 2002; Sridhara, 2013). This variant is reported in ClinVar (Variation ID: 6896) and is observed in the general population databases at a low frequency of 0.002 percent (5/277172 alleles, Genome Aggregation Database). The proline at codon 81 is well conserved across a variety of species and computational algorithms (SIFT, PolyPhen2, MutationTaster) which predict this variant to be damaging to the protein. Based on the above information, this variant is considered pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should

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

be offered testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report.

REFERENCES
Baysal BE, et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. Science. 2000;287(5454):848-51.

Baysal BE, et al. Prevalence of SDHB, SDHC, and SDHD germline mutations in clinic patients with head and neck paragangliomas. J Med Genet. 2002;39(3):178-83.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and adrenal tumors. (https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf)

Sridhara SK, et al. Genetic testing in head and neck paraganglioma: who, what, and why? J Neurol Surg B Skull Base. 2013;74(4):236-40.

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	22-054-106933	2/23/2022 12:00:00 PM	2/23/2022 12:02:31 PM	2/23/2022 12:22:00 PM
SDH Interp	22-054-106933	2/23/2022 12:00:00 PM	2/23/2022 12:02:31 PM	2/23/2022 12:22:00 PM

END OF CHART

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