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

Physician: Doctor, Example

Patient: Patient, Example

DOB	9/21/1981
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

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

ARUP test code 2007167

HPGL-PCC (SDHB,C,D) Seq, DelDup Specimen	Whole Blood	
HPGL-PCC (SDHB,C,D) Seq, DelDup Interp	**Positive**	*

H – high L – low * – abnormal C – critical

TEST PERFORMED - 2007167
TEST DESCRIPTION - Hereditary Paraganglioma-Pheochromocytoma (SDHB, SDHC, and SDHD) Sequencing and Deletion/Duplication Panel
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the SDHD gene.

Gene: SDHD
Nucleic Acid Change: c.242C>T; Heterozygous
Amino Acid Alteration: p.Pro81Leu

INTERPRETATION
One copy of a pathogenic variant, c.242C>T; p.Pro81Leu, was detected in the SDHD gene by sequencing. This result is consistent with a diagnosis of Hereditary Paraganglioma-Pheochromocytoma Syndrome type 1 (PGL1). Disease manifestations are variable and generally only occur when pathogenic variants in SDHD are inherited paternally due to a parent-of-origin effect. This individual's offspring have a 50 percent risk of inheriting the causative pathogenic variant. No pathogenic variants were detected by deletion/duplication analysis in SDHD, nor by sequence and deletion/duplication analyses in SDHB and SDHC.

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) predict this variant to be damaging to the protein. Taken together, this variant is considered pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered targeted testing for the identified variant (Familial Mutation, Targeted Sequencing; ARUP test code 2001961).

COMMENTS
Reference Sequences: GenBank # NM_003000.2 (SDHB), NM_003001.3 (SDHC), NM_003002.2 (SDHD)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Benign variants are not included in this report but are available upon request.

REFERENCES
Link to ClinVar database for p.Pro81Leu:
https://www.ncbi.nlm.nih.gov/clinvar/variation/6896/

Baysal BE et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. Science. 2000 Feb 4;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 Mar;39(3):178-83.

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

This result has been reviewed and approved by Pinar Bayrak-Toydemir, M.D., Ph.D.

H – high L – low * – abnormal C – critical

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

CHARACTERISTICS: Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are characterized by paragangliomas (neuroendocrine tumors of the autonomic nervous system) and pheochromocytomas (paragangliomas of the adrenal medulla). Pathogenic germline mutations in a number of genes, including SDHB, SDHC, and SDHD, predispose to paraganglioma and pheochromocytoma with risk of malignant transformation.
INCIDENCE: About 1 in 300,000 per year.
INHERITANCE: Autosomal dominant; parent of origin effect for SDHD.
CAUSE: Pathogenic succinate dehydrogenase, subunits B, C, and D (SDHB, SDHC, and SDHD) gene mutations. Mutations in other genes, including TMEM127, EGLN1, MAX, SDHA, and SDHAF2, may also be causative.
CLINICAL SENSITIVITY: 26-30 percent.
METHODOLOGY: Bidirectional sequencing of all coding regions and intron-exon boundaries of the SDHB, SDHC, and SDHD genes; Multiplex Ligation-dependent Probe Amplification (MLPA) to detect large SDHB, SDHC, and SDHD deletions /duplications.
ANALYTICAL SENSITIVITY AND SPECIFICITY: Sequencing: 99 percent; MLPA: 90 and 99 percent, respectively.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations and deep intronic mutations will not be detected. The breakpoints of large deletions/duplications will not be determined. Mutations in genes other than SDHB, SDHC, and SDHD are not evaluated.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
HPGL-PCC (SDHB,C,D) Seq, DelDup Specimen	17-170-113700	6/19/2017 9:38:00 AM	6/20/2017 2:20:46 PM	7/11/2017 4:30:23 PM
HPGL-PCC (SDHB,C,D) Seq, DelDup Interp	17-170-113700	6/19/2017 9:38:00 AM	6/20/2017 2:20:46 PM	7/11/2017 4:30:23 PM

END OF CHART

H – high L – low * – abnormal C – critical