ARUP LABORATORIES | www.aruplab.com
500 Chipeta Way, Salt Lake City, Utah 84108-1221
phone: (801) 583-2787, toll free: (800) 522-2787
Julio C. Delgado, MD, MS, Director of Laboratories

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/1752
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Hereditary Paraganglioma-Pheochromocytoma (SDHD) Sequencing and Deletion/Duplication

ARUP test code 2007122

HPGL-PCC (SDHD) Seq, DelDup Specimen	Whole Blood	
HPGL-PCC (SDHD) Seq, DelDup Interp	**Positive**	*

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

TEST PERFORMED - 2007122
TEST DESCRIPTION - Hereditary Paraganglioma-Pheochromocytoma (SDHD) Sequencing and Deletion/Duplication
INDICATION FOR TEST - Predictive Testing

RESULT
One pathogenic variant detected in the SDHD gene.

DNA VARIANT(S)
Pathogenic
Nucleic Acid Change: c.242C>T; Heterozygous
Amino Acid Alteration: p.Pro81Leu

INTERPRETATION
One pathogenic variant, c.242C>T; p.Pro81Leu, was detected in the SDHD gene by sequencing. The p.Pro81Leu variant has been reported in several familial and sporadic cases of paraganglioma (PGL) (Baysal 2000, Baysal 2002, Sridhara 2013). This variant is reported in the dbSNP variant database (rs80338844) but has not been reported in general population databases (Exome Variant Server, Exome Aggregation Consortium). The proline residue is well conserved across a variety of species and computational analyses (SIFT, PolyPhen2, MutationTaster) predict this variant to be damaging to the protein. Taken together, this variant is considered pathogenic.

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 variant.

No pathogenic variants were detected by deletion/duplication analysis.

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 pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Reference Sequence: GenBank # NM_003002.2 (SDHD)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Benign variants are not included on this report but are available upon request.

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

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

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

This result has been reviewed and approved by Elaine Lyon, Ph.D.

BACKGROUND INFORMATION: Hereditary Paraganglioma-Pheochromocytoma (SDHD) Sequencing and Deletion/Duplication

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 SDHD, predispose to paraganglioma and pheochromocytoma.
INCIDENCE: About 1 in 300,000 per year.
INHERITANCE: Autosomal dominant; disease manifestations generally occur when mutations in SDHD are inherited from the father (but not from the mother) due to a parent of origin effect.
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: 15 percent.
METHODOLOGY: Bidirectional sequencing of all coding regions and intron-exon boundaries of the SDHD gene; multiplex ligation-dependent probe amplification (MLPA) to detect large 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 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 (SDHD) Seq, DelDup Specimen	17-017-111123	1/17/2017 1:41:00 PM	1/17/2017 1:41:25 PM	3/8/2017 1:15:32 PM
HPGL-PCC (SDHD) Seq, DelDup Interp	17-017-111123	1/17/2017 1:41:00 PM	1/17/2017 1:41:25 PM	3/8/2017 1:15:32 PM

END OF CHART