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 (SDHC) Sequencing and Deletion/Duplication

ARUP test code 2007117

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

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

TEST PERFORMED - 2007117
TEST DESCRIPTION - Hereditary Paraganglioma-Pheochromocytoma (SDHC) Sequencing and Deletion/Duplication
INDICATION FOR TEST - Predictive Testing

RESULT
One pathogenic variant detected in the SDHC gene.

DNA VARIANT(S)
Pathogenic
Nucleic Acid Change: c.387G>A; Heterozygous
Amino Acid Alteration: p.Trp129Ter

INTERPRETATION
One pathogenic variant, c.387G>A; p.Trp129Ter, was detected in the SDHC gene by sequencing. The variant has not been reported in the medical literature or gene-specific databases, listed in the general population databases (1000 Genomes Project, Exome Variant Server, Exome Aggregation Consortium), nor previously identified in our laboratory. However, a truncating variant downstream (c.397C>T, p.Arg133Ter) has been reported in patients diagnosed with paraganglioma (Zbuk 2007, Bickmann 2014), though with incomplete penetrance (Bickmann 2014). The c.387G>A variant introduces a nonsense codon at amino acid position 129, and is predicted to result in a truncated protein or an absent transcript. Based on the above evidence, the variant is classified as pathogenic. This result is consistent with a diagnosis of Hereditary Paraganglioma-Pheochromocytoma Syndrome type 3 (PGL3); clinical manifestations are variable. 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 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Reference Sequence: GenBank # NM_003001.3 (SDHC)
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
Bickmann J et al. (2014) Phenotypic variability and risk of malignancy in SDHC-linked paragangliomas: lessons from three unrelated cases with an identical germline mutation (p.Arg133*). J Clin Endocrinol Metab. 99(3):E489-96.
Zbuk K et al. (2007) Germline mutations in PTEN and SDHC in a woman with epithelial thyroid cancer and carotid paraganglioma. Nat Clin Pract Oncol. 4(10):608-12.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Hereditary Paraganglioma-Pheochromocytoma (SDHC) 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 SDHC, predispose to paraganglioma and pheochromocytoma.
INCIDENCE: About 1 in 300,000 per year.
INHERITANCE: Autosomal dominant.
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: 4 percent.
METHODOLOGY: Bidirectional sequencing of all coding regions and intron-exon boundaries of the SDHC gene; multiplex ligation-dependent probe amplification (MLPA) to detect large SDHC 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 SDHC 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 (SDHC) Seq, DelDup Specimen	17-017-110838	1/17/2017 1:33:00 PM	1/17/2017 1:33 26 PM	3/8/2017 1:15:00 PM
HPGL-PCC (SDHC) Seq, DelDup Interp	17-017-110838	1/17/2017 1:33:00 PM	1/17/2017 1:33 26 PM	3/8/2017 1:15:00 PM

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