ARUP LABORATORIES
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Tracy I. George, MD, Chief Medical Officer

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

Legius Syndrome (SPRED1) Sequencing and Deletion/Duplication

ARUP test code 2008347

Legius Syndrome (SPRED1)Seq, DelDup Spcm	Whole Blood	
Legius Syndrome (SPRED1)Seq, DelDup Int	Positive	*

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

TEST PERFORMED - 2002945
TEST DESCRIPTION - Legius Syndrome (SPRED1) Sequencing and Deletion/Duplication
INDICATION FOR TEST - Not Provided

RESULT
One pathogenic variant was detected in the SPRED1 gene.

DNA VARIANT(S)
Variant Classification: Pathogenic
Gene: SPRED1
Nucleic Acid Change: c.349C>T; Heterozygous
Amino Acid Alteration: p.Arg117Ter

INTERPRETATION
One pathogenic variant, c.349C>T; p.Arg117Ter, was detected in the SPRED1 gene by sequencing. This result is consistent with a diagnosis of Legius syndrome; clinical manifestations are variable and age-dependent. This individual's offspring have a 50 percent chance of inheriting the causative variant.

No pathogenic variants were detected by deletion/duplication analysis

Evidence for variant classification(s): The p.Arg117Ter variant has been described in the literature in individuals and families with Noonan-like syndrome of Legius syndrome (Brems, 2007; Cemeli-Cano, 2014; Sakai, 2015). The variant has been described in the dbSNP database without a minor allele frequency and has not been described in the Exome Variant Server or the Exome Aggregation Consortium. The p.Arg117Ter variant induces a premature termination codon and is predicted to result in a truncated protein or absent transcript and is therefore considered pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered a clinical evaluation for Legius syndrome. If it is unclear whether or not they are affected, targeted testing for the identified variant should be considered (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Reference Sequence: GenBank # NM_152594.2 (SPRED1)
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
Cemeli-Cano M et al. (2014) A novel neurocutaneous syndrome: Legius syndrome. A case report. Rev Neurol. 59(5):209-12.

Brems H et al. (2007) Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. Nat Genet. 39(9):1120-6.

Sakai N et al. (2015) Family with Legius syndrome (neurofibromatosis type 1-like syndrome). J Dermatol. 42(7):703-5.

This result has been reviewed and approved by [redacted]

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BACKGROUND INFORMATION: Legius Syndrome (SPRED1) Sequencing and Deletion/Duplication

CHARACTERISTICS: Cafe au lait spots, axillary and inguinal freckling, learning disabilities and macrocephaly. Neurofibromas, lisch nodules and CNS tumors are not observed.
INCIDENCE: Unknown; may represent 0.5 percent of neurofibromatosis type 1 diagnoses or 8 percent of those with isolated cafe au lait spots.
INHERITANCE: Autosomal dominant.
CAUSE: Pathogenic SPRED1 gene mutations.
CLINICAL SENSITIVITY: Unknown.
METHODOLOGY: Bidirectional sequencing and multiplex ligation-dependent probe amplification (MLPA) of the entire coding region and intron-exon boundaries of the SPRED1 gene.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations and deep intronic mutations will not be detected. Deletion/duplication breakpoints will not be determined.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online at www.aruplab.com.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Legius Syndrome (SPRED1)Seq, DelDup Spcm	17-017-112887	1/17/2017 2:29:00 PM	1/17/2017 2:30:19 PM	4/18/2017 3:50:00 PM
Legius Syndrome (SPRED1)Seq, DelDup Int	17-017-112887	1/17/2017 2:29:00 PM	1/17/2017 2:30:19 PM	4/18/2017 3:50:00 PM

END OF CHART

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