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

Physician: Doctor, Example

Patient: Patient, Example

DOB	3/9/2023
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Neurofibromatosis Type 1 and Legius Syndrome Panel, Sequencing and Deletion/Duplication

ARUP test code 3003927

NF1 and LS (SPRED1) Panel Specimen: Whole Blood

NF1 and LS (SPRED1) Panel Interpretation: Positive

RESULT
One pathogenic variant was detected in the NF1 gene.

PATHOGENIC VARIANT
Gene: NF1 (NM_001042492.3)
Nucleic Acid Change: c.6852_6855del; Heterozygous
Amino Acid Alteration: p.Tyr2285ThrfsTer5
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.6852_6855del; p.Tyr2285ThrfsTer5, was detected in the NF1 gene by massively parallel sequencing. Pathogenic NF1 variants are inherited in an autosomal dominant manner, and are associated with neurofibromatosis type 1 (MIM: 162200; OMIM (R)).This result is consistent with a diagnosis of neurofibromatosis type 1; clinical manifestations are variable and age-dependent. This individual's future offspring have a 50 percent chance of inheriting the causative variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The NF1 c.6852_6855delTTAC; p.Tyr2285fs variant (rs863224836 ClinVar Variation ID: 24866), also known as c.6789_6792delTTAC for NM_000267.3, is reported in the literature in multiple individuals and families affected with neurofibromatosis type 1 (Banerjee 2017, Brems 2009, Griffiths 2007, Lee 2006, Robinson 1995), and a family affected with neurofibromatosis-Noonan syndrome (Ekvall 2014). This variant is absent from the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. This variant causes a frameshift by deleting 4 nucleotides, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be 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 neurofibromatosis type 1. If it is unclear whether or not they are affected, testing should be offered for the identified pathogenic NF1 variant (Familial Targeted Sequencing, ARUP test code 3005867).

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

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations: None

REFERENCES
OMIM(R) Copyright (C) 1996 - Present year, Johns Hopkins University All rights reserved.
Banerjee S et al. Novel phenotypes of NF1 patients from unrelated Chinese families with tibial pseudarthrosis and anemia. Oncotarget. 2017 Jun 13;8(24):39695-39702. PMID: 27980226

Brems H et al. Glomus tumors in neurofibromatosis type 1: genetic, functional, and clinical evidence of a novel association. Cancer Res. 2009 Sep 15;69(18):7393-401. PMID: 19738042

Ekvall S et al. Novel association of neurofibromatosis type 1-causing mutations in families with neurofibromatosis-Noonan syndrome. Am J Med Genet A. 2014 Mar;164A(3):579-87. PMID: 24357598

Griffiths S et al. Molecular diagnosis of neurofibromatosis type 1: 2 years experience. Fam Cancer. 2007;6(1):21-34. PMID: 16944272

Lee MJ et al. Identification of forty-five novel and twenty-three known NF1 mutations in Chinese patients with neurofibromatosis type 1. Hum Mutat. 2006 Aug;27(8):832. PMID: 16835897

Robinson PN et al. Two recurrent nonsense mutations and a 4 bp deletion in a quasi-symmetric element in exon 37 of the NF1 gene. Hum Genet. 1995 Jul;96(1):95-8. PMID: 7607663

This result has been reviewed and approved by [redacted] M.D., Ph.D.

BACKGROUND INFORMATION: Neurofibromatosis Type 1 and Legius Syndrome Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Common clinical findings of neurofibromatosis type 1 (NF1) include cafe au lait macules, axillary and inguinal freckling, cutaneous fibromas, Lisch nodules, choroidal freckling, and learning disabilities. Less common findings of NF1 include optic or other CNS gliomas, vasculopathies, tibial pseudarthrosis, scoliosis, somatic overgrowth, and malignant peripheral nerve sheath tumors. The following symptoms of Legius syndrome (LS) overlap with findings in NF1: cafe au lait spots, axillary and inguinal freckling, learning disabilities, ADHD, developmental delays, and macrocephaly. Neurofibromas, Lisch nodules, and CNS tumors are not typically observed in LS.

EPIDEMIOLOGY: Incidence of NF1 is 1 in 3,000. Prevalence of LS is estimated at 1 in 46,000-75,000.

CAUSE: Pathogenic germline variants in the NF1 gene (for NF1) or SPRED1 gene (for LS).

INHERITANCE: Autosomal dominant; 50 percent of pathogenic NF1 variants are de novo.

PENETRANCE: Complete after childhood for NF1.

CLINICAL SENSITIVITY: Approximately 90 percent for NF1 and 99 percent for LS.

GENES TESTED: NF1 (NM_001042492); SPRED1 (NM_152594)

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. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

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. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of NF1 or LS. This test only detects variants within the coding regions and intron-exon boundaries of the NF1 and SPRED1 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. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. 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.

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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
NF1 and LS (SPRED1) Panel Specimen	24-262-401012	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
NF1 and LS (SPRED1) Panel Interpretation	24-262-401012	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

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