Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: TEST,

Patient: NF1 NGS, POS

DOB
Sex: Male
Patient Identifiers: 44131
Visit Number (FIN): 44457
Collection Date: 11/14/2022 11:13

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_001042492.2)
Nucleic Acid Change: c.1756_1759delACTA; heterozygous
Amino Acid Alteration: p.Thr586ValfsTer18
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.1756_1759delACTA; p.Thr586ValfsTer18, was detected in the NF1 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic NF1 variants are inherited in an autosomal dominant manner and are associated with neurofibromatosis type 1 (MIM: 162200). This result is consistent with a diagnosis of neurofibromatosis type 1; clinical manifestations are variable and age dependent. This individual's 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.1756_1759delACTA; p.Thr586ValfsTer18 variant (rs786202782), also known as 1754_1757del, has been described in several individuals with a diagnosis of neurofibromatosis type 1, including the variant occurring de novo in at least one individual (Anastasaki, 2017; Chai, 2019; Corsello, 2018; Froukh, 2020; Park, 1998; Pemov, 2017). The variant is reported as pathogenic by several sources in the ClinVar database (Variation ID: 186215) and is only observed on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism. This variant causes a frameshift by deleting four 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 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 for the identified pathogenic variant should be offered (Familial Targeted Sequencing, ARUP test code 3005867).

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

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Anastasaki C, et al. Children with 5'-end NF1 gene mutations are more likely to have glioma. Neurol Genet. 2017;3(5):e192.

Chai P, et al. Clinical characteristics and mutation Spectrum of NF1 in 12 Chinese families with orbital/periorbital plexiform Neurofibromatosis type 1. BMC Med Genet. 2019;20(1):158.

Corsello G, et al. Clinical and molecular characterization of 112 single-center patients with Neurofibromatosis type 1. Ital J Pediatr. 2018;44(1):45.

Froukh T, et al. Genetic basis of neurodevelopmental disorders in 103 Jordanian families. Clin Genet. 2020;97(4):621-627.

Park VM, et al. Neurofibromatosis type 1 (NF1): a protein truncation assay yielding identification of mutations in 73% of patients. J Med Genet. 1998;35(10):813-820.

Pemov A, et al. The primacy of NF1 loss as the driver of tumorigenesis in neurofibromatosis type 1-associated plexiform neurofibromas. Oncogene. 2017;36(22):3168-3177.

This result has been reviewed and approved by Rong Mao, MD.
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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
NF1 and LS (SPRED1) Panel Specimen	22-318-105100	11/14/2022 11:13:00 AM	11/14/2022 11:14:36 AM	11/14/2022 11:19:00 AM
NF1 and LS (SPRED1) Panel Interpretation	22-318-105100	11/14/2022 11:13:00 AM	11/14/2022 11:14:36 AM	11/14/2022 11:19:00 AM

END OF CHART

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