ARUP LABORATORIES
800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Jonathan R. Genzen, MD, PhD, Chief Medical Officer

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	9/18/1983
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Cystic Fibrosis (CFTR) Sequencing and Deletion/Duplication

ARUP test code 3004745

CFTR Specimen	Whole Blood

CFTR Interp

Positive

RESULT
One pathogenic variant and one pathogenic variant of varying clinical consequences and one variant of uncertain significance were detected in the CFTR gene.

PATHOGENIC VARIANT
Gene: CFTR (NM_000492.3)
Nucleic Acid Change: c.1521_1523del; Heterozygous
Amino Acid Alteration: p.Phe508del
Inheritance: Autosomal recessive

PATHOGENIC VARIANT - VARYING CLINICAL CONSEQUENCES
Gene: CFTR (NM_000492.3)
Nucleic Acid Change: 13TG-5T; Heterozygous
Inheritance: Autosomal recessive

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: CFTR (NM_000492.4)
Nucleic Acid Change: c.3705T>G; Heterozygous
Amino Acid Alteration: p.Ser1235Arg
Inheritance: Autosomal Recessive

INTERPRETATION
According to information available to ARUP, this individual has bronchiectasis, chronic cough, and history of pneumonia and hemoptysis. Previous genetic testing has reportedly revealed one copy of the CFTR F508del variant. One copy of a pathogenic variant, c.1521_1523del; p.Phe508del, was detected by Sanger sequencing, and one copy of a pathogenic variant of varying clinical consequences, 13TG-5T, was detected by Sanger sequencing in the CFTR gene. The p.Phe508del variant is almost exclusively found on the same chromosome as 10TG-9T (Raraigh 2022); therefore the identified variants are likely to be on opposite chromosomes. This molecular result may cause cystic fibrosis (CF), a CFTR-related disorder (e.g., pancreatitis, lung disease, or bilateral absence of the vas deferens), or no symptoms. Because of this variability, clinical criteria alone should be used to determine whether this individual has CF (CFTR2 database).

In addition, one copy of a variant of uncertain significance, c.3705T>G; p.Ser1235Arg, was detected by massively parallel sequencing in the CFTR gene. However, it is uncertain whether this variant is disease-associated or benign.

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

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The CFTR c.1521_1523del; p.Phe508del (F508del) variant is the most common pathogenic CFTR variant that has been reported in Caucasians (Sosnay 2013, CFTR2 database). This variant is considered to cause cystic fibrosis when identified with another pathogenic variant on the opposite chromosome.

The CFTR 13TG-5T variant is reported in patients diagnosed with cystic fibrosis or congenital bilateral absence of vas deferens (Groman 2004, Lin 2008, CFTR2 database). Functional characterization of the variant indicates a reduction in the full-length CFTR mRNA, with increased incidence of exon 9 being skipped due to aberrant splicing (Hefferon 2004). Based on available information, this variant is considered to be pathogenic with varying clinical consequences.

The CFTR c.3705T>G; p.Ser1235Arg variant (rs34911792) is historically considered to be mildly pathogenic due to its prevalence in patients diagnosed with mild respiratory disorders (Rene 2011) or chronic pancreatitis (Hamoir 2013, Steiner 2011, Weiss 2005). However, genotype-phenotype studies indicate that the variant is observed at similar frequencies between affected and asymptomatic individuals (LaRusch 2014, Monaghan 2000, Rene 2011, Sosnay 2013). Functional studies also indicate no defect in CFTR maturation or chloride transport activity (Sosnay 2013, Van Goor 2014). The variant is listed in ClinVar (Variation ID: 35872) and is observed in the general population at an overall frequency of 0.5% (1,409/279,632 alleles, including 4 homozygotes) in the Genome Aggregation Database (v2.1.1). Computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.531). Current evidence indicates that this variant, when present with a pathogenic CFTR variant on the opposite chromosome, is not associated with classic cystic fibrosis. However, it remains uncertain whether it may contribute to the clinical phenotype in individuals with milder CFTR-related disease (e.g., an isolated presentation of pancreatitis, congenital bilateral absence of the vas deferens, or mild lung disease).

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical management and screening. Targeted sequencing for both identified variants is recommended for this individual's parents and symptomatic siblings. Other adult family members should be offered carrier testing for the variant identified in their family lineage. This individual's reproductive partner should be offered carrier testing for CF (Cystic Fibrosis 165 Pathogenic Variants, ARUP test code 2013661). Surveillance of medical literature regarding the variant of uncertain significance is recommended.

COMMENTS
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
Link to CFTR2 database: http://cftr2.org/
Groman J et al. Variation in a repeat sequence determines whether a common variant of the cystic fibrosis transmembrane conductance regulator gene is pathogenic or benign. Am J Hum Genet. 2004 74(1):176-9.
Hefferon T et al. A variable dinucleotide repeat in the CFTR gene contributes to phenotype diversity by forming RNA secondary structures that alter splicing. Proc Natl Acad Sci U S A. 2004 101(10):3504-9.
Hamoir C et al. Clinical and morphological characteristics of sporadic genetically determined pancreatitis as compared to

idiopathic pancreatitis: higher risk of pancreatic cancer in CFTR variants. Digestion. 2013; 87(4):229-39. PMID: 23751316.
LaRusch J et al. Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. PLoS Genet. 2014; 10(7):e1004376. PMID: 25033378.
Lin C et al. Phenotype and genotype of two Taiwanese cystic fibrosis siblings and a survey of delta F508 in East Asians. Pediatr Neonatol. 2008 49(6):240-4.
Monaghan K et al. Frequency and clinical significance of the S1235R mutation in the cystic fibrosis transmembrane conductance regulator gene: results from a collaborative study. Am J Med Genet. 2000; 95(4):361-5. PMID: 11186891.
Raraigh KS et al. Complete CFTR gene sequencing in 5,058 individuals with cystic fibrosis informs variant-specific treatment. J Cyst Fibros. 2022 May;21(3):463-470. PMID: 34782259.
Rene C et al. p.Ser1235Arg should no longer be considered as a cystic fibrosis mutation: results from a large collaborative study. Eur J Hum Genet. 2011; 19(1):36-42. PMID: 20717170.
Sosnay PR et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Genet. 2013; 45(10):1160-7. PMID: 23974870.
Steiner B et al. Common CFTR haplotypes and susceptibility to chronic pancreatitis and congenital bilateral absence of the vas deferens. Hum Mutat. 2011; 32(8):912-20. PMID: 21520337.
Van Goor F et al. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. J Cyst Fibros. 2014; 13(1):29-36. PMID: 23891399.
Weiss F et al. Complete cystic fibrosis transmembrane conductance regulator gene sequencing in patients with idiopathic chronic pancreatitis and controls. Gut. 2005; 54(10):1456-60. PMID: 15987793.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Cystic Fibrosis (CFTR) Sequencing and Deletion/Duplication

CHARACTERISTICS: Cystic fibrosis (CF) and CFTR-related disorders are caused by biallelic pathogenic variants in the CFTR gene. Age of onset, manifestations, and symptom severity vary greatly. Symptoms of classic CF include chronic sinopulmonary disease, pancreatic insufficiency, hepatic disease, prolapsed rectum, meconium ileus, obstructive azoospermia, and salt loss syndromes. CFTR-related disorders are less severe and may be characterized by isolated pancreatitis, bilateral absence of the vas deferens, chronic bronchiectasis, and/or nasal polyposis.

EPIDEMIOLOGY: CF is more common in individuals of Ashkenazi Jewish and Caucasian/White descent (approximately 1 in 2,300 and 1 in 2,500 individuals, respectively). CF is less common in individuals of Hispanic, African American/Black, and Asian American descent (approximately 1 in 13,500, 1 in 15,100, and 1 in 35,100, respectfully).

CAUSE: Biallelic pathogenic variants in the CFTR gene

INHERITANCE: Autosomal recessive

CLINICAL SENSITIVITY: 99 percent

GENE TESTED: CFTR (NM_000492)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the CFTR gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage or known low quality, 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 CFTR gene. 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 two exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of three 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 CF. This test only detects variants within the coding regions and intron-exon boundaries of the CFTR gene. 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 two 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
CFTR Specimen	24-311-129017	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
CFTR Interp	24-311-129017	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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