

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

Physician: Doctor, Example

Patient: Patient, Example

DOB: 4/2/1953
Gender: Male
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
Collection Date: 00/00/0000 00:00

Cystic Fibrosis (CFTR) Sequencing with Reflex to Deletion/Duplication (Temporary Referral as of 12/07/20)

ARUP test code 0051640

Cystic Fibrosis Seq, w/Rflx DelDup Spec whole blood

Cystic Fibrosis Seq, w/Rflx DelDup Int

Positive *

TEST PERFORMED - 0051640
TEST DESCRIPTION - Cystic Fibrosis (CFTR) Sequencing with Reflex to Deletion/Duplication
INDICATION FOR TEST - Confirm Diagnosis

RESULT

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

DNA VARIANTS

Classification: Pathogenic
Gene: CFTR
Nucleic Acid Change: c.1521_1523delCTT; Heterozygous
Amino Acid Alteration: p.Phe508del

Classification: Pathogenic - Varying Clinical Consequences
Gene: CFTR
Nucleic Acid Change: c.3454G>C; Heterozygous
Amino Acid Alteration: p.Asp1152His

INTERPRETATION

One copy of a pathogenic variant, c.1521_1523delCTT; p.Phe508del, and one copy of a variant of varying clinical consequences, c.3454G>C; p.Asp1152His, were detected in the CFTR gene by sequencing. If these variants occur 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).

CFTR deletion/duplication analysis was not performed.

Evidence for variant classifications: The CFTR 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 c.3454G>C; p.Asp1152His variant (rs75541969) is reported in the literature in multiple individuals affected with classic cystic fibrosis or CFTR-related disorders (Chillon 1995,

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

Gallati 2009, Highsmith 2005, LaRusch 2014, Masson 2013, Steiner 2011, Sosnay 2013, CFTR2 database). This variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 35867), and is found in the general population with an overall allele frequency of 0.038% (104/276606 alleles) in the Genome Aggregation Database. The aspartic acid at codon 1152 is moderately conserved, and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. Functional characterization of the variant protein indicates a significant reduction in chloride and bicarbonate transport activity (LaRusch 2014, Sosnay 2013, Van Goor 2014, Vankeerberghen 1998). Genotype-phenotype correlation studies have demonstrated that this variant, in combination with another pathogenic CFTR variant (e.g. p.Phe508del), is associated with highly variable clinical presentations, ranging from asymptomatic to pancreatic insufficient CF (Burge1 2010, Mussaffi 2006, Terlizzi 2015, CFTR2 database). Based on available information, the p.Asp1152His variant is classified as pathogenic with variable presentation of clinical phenotypes.

RECOMMENDATIONS

Genetic consultation is indicated, including a discussion of medical screening and management. Targeted sequencing for both identified variants is recommended for this individual's parents and symptomatic siblings (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). 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 (Cystic Fibrosis 165 Pathogenic Variants, ARUP test code 2013661).

COMMENTS

Reference Sequence: GenBank # NM_000492.3 (CFTR)
Nucleotide numbering begins at the "A" of the ATG initiation codon.

Likely benign and benign variants are not reported.

REFERENCES

CFTR2 database: <http://cftr2.org/>

Burge1 P et al. Non-classic cystic fibrosis associated with D1152H CFTR mutation. Clin Genet. 2010; 77(4):355-64.

Chillon M et al. Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. N Engl J Med. 1995; 332(22):1475-80.

Gallati S et al. Cystic fibrosis transmembrane conductance regulator mutations in azoospermic and oligospermic men and their partners. Reprod Biomed Online. 2009; 19(5):685-94.

Highsmith WE Jr et al. A CFTR mutation (D1152H) in a family with mild lung disease and normal sweat chlorides. Clin Genet. 2005; 68(1):88-90.

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.

Masson E et al. A conservative assessment of the major genetic causes of idiopathic chronic pancreatitis: data from a comprehensive analysis of PRSS1, SPINK1, CTFC and CFTR genes in 253 young French patients. PLoS One. 2013; 8(8):e73522.

Mussaffi H et al. Cystic fibrosis mutations with widely variable phenotype: the D1152H example. Pediatr Pulmonol. 2006; 41(3):250-4.

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.

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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.

Terlizzi V et al. Clinical expression of patients with the D1152H CFTR mutation. J Cyst Fibros. 2015; 14(4):447-52.

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.

Vankeerberghen A et al. Characterization of 19 disease-associated missense mutations in the regulatory domain of the cystic fibrosis transmembrane conductance regulator. Hum Mol Genet. 1998; 7(11):1761-9.

This result has been reviewed and approved by [REDACTED]

BACKGROUND INFORMATION: Cystic Fibrosis (CFTR) Sequencing with Reflex to Deletion/Duplication
CHARACTERISTICS: Chronic sino-pulmonary disease, gastrointestinal malabsorption/pancreatic insufficiency, and obstructive azoospermia. Findings are often limited to a single organ system such as isolated pancreatitis, bilateral absence of the vas deferens, nasal polyposis, or bronchiectasis in non-classic cystic fibrosis (CF).
INCIDENCE OF CLASSIC CF: 1 in 3,000 Caucasians or Ashkenazi Jewish, 1 in 8,000 Hispanics, 1 in 15,000 African Americans, 1 in 32,000 Asians.
INCIDENCE OF NONCLASSIC CF: Unknown.
INHERITANCE: Autosomal recessive.
PENETRANCE: High for severe mutations, variable for mild/moderate mutations.
CAUSE OF CLASSIC CF: Two deleterious CFTR mutations on opposite chromosomes.
CAUSE OF NONCLASSIC CF: Typically one severe and one mild/moderate CFTR mutations on opposite chromosomes.
MUTATIONS TESTED: Base pair substitutions and deletions/duplications within the coding region and intron-exon boundaries; additionally, two deep intronic mutations (3849+10kbC>T and 1811+1.6kba>G).
CLINICAL SENSITIVITY: 99 percent.
METHODOLOGY FOR SEQUENCING: Bidirectional sequencing of the entire CFTR coding region, intron-exon boundaries and two deep intronic mutations.
METHODOLOGY FOR DELETION/DUPLICATION: Multiplex ligation-dependent probe amplification (MLPA) to detect large CFTR coding region deletions/duplications.
ANALYTICAL SENSITIVITY AND SPECIFICITY FOR SEQUENCING: 99 percent.
ANALYTICAL SENSITIVITY AND SPECIFICITY FOR MLPA: 98 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Breakpoints for large deletions/duplications will not be determined. Regulatory region and some deep intronic mutations will not be detected.

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

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Cystic Fibrosis Seq, w/Rflx DelDup Spec	20-316-103179	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cystic Fibrosis Seq, w/Rflx DelDup Int	20-316-103179	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

Unless otherwise indicated, testing performed at:

ARUP LABORATORIES | 800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Tracy I. George, MD, Laboratory Director

Patient: Patient, Example
ARUP Accession: 20-316-103179
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
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