

Cystic Fibrosis (*CFTR*), 165 Pathogenic Variants with Reflex to Sequencing and Reflex to Deletion/Duplication

Indications for Ordering

For individuals with suspected cystic fibrosis (CF) or a *CFTR*-related disorder

Test Description

- Polymerase chain reaction followed by fluorescence monitoring of 165 pathogenic *CFTR* gene variants (see table)
- Bidirectional sequencing of the *CFTR* coding regions and intron/exon boundaries
- Deletion/duplication analysis by multiplex ligation-dependent probe amplification

Tests to Consider

Primary tests

[Cystic Fibrosis \(*CFTR*\) 165 Pathogenic Variants with Reflex to Sequencing and Reflex to Deletion/Duplication 2013664](#)

- For individuals with suspected CF
- This test is NOT indicated for routine obstetric carrier screening
- If individual is not symptomatic, order the CF 165 pathogenic variants test

[Cystic Fibrosis \(*CFTR*\) 165 Pathogenic Variants with Reflex to Sequencing 2013663](#)

- For individuals with suspected CF
- This test is NOT indicated for routine obstetric carrier screening
- If individual is not symptomatic, order the CF 165 pathogenic variants test

Related tests

[Cystic Fibrosis \(*CFTR*\) 165 Pathogenic Variants 2013661](#)

- Carrier screening for expectant individuals and those planning a pregnancy
- Diagnostic testing for individuals with symptoms of classic CF

[Cystic Fibrosis \(*CFTR*\) Sequencing 0051110](#)

- For individuals with suspected CF but without 2 pathogenic variants detected by the CF 165 pathogenic variants test
- This test is NOT indicated for routine obstetric carrier screening

[Cystic Fibrosis \(*CFTR*\) Sequencing with Reflex to Deletion/Duplication 0051640](#)

- For individuals with suspected CF but without 2 pathogenic variants detected by the CF 165 pathogenic variants test
- This test is NOT indicated for routine obstetric carrier screening

[Cystic Fibrosis \(*CFTR*\) 165 Pathogenic Variants, Fetal 2013662](#)

- For fetal testing when both parents are known carriers of one of the variants on the CF 165 pathogenic variants test or fetus has an echogenic bowel

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful when a pathogenic familial variant identifiable by sequencing is known

[Deletion/Duplication Analysis by MLPA 3003144](#)

- Useful when a large familial *CFTR* gene deletion/duplication is known
- Useful for individuals without an identifiable *CFTR* gene variant by sequence analysis

Disease Overview

Incidence

- Classic CF (Abeliovich, 1992)
 - Ashkenazi Jews: 1/2,300
 - Caucasians: 1/2,500
 - Hispanic Americans: 1/13,500
 - African Americans: 1/15,100
 - Asian Americans: 1/35,100
- Other *CFTR*-related disorders: unknown

Symptoms

- Classic CF
 - Chronic sinopulmonary disease and infections
 - Pancreatic insufficiency (endocrine and exocrine)
 - Hepatic disease: biliary obstruction and portal fibrosis
 - Prolapsed rectum
 - Failure to thrive
 - Meconium ileus
 - Obstructive azoospermia
 - Salt loss syndromes
 - Life expectancy: ~41 years

- *CFTR*-related disorders
 - Idiopathic pancreatitis
 - Bilateral absence of the vas deferens (BAVD)
 - Bronchiectasis
 - Nasal polyposis
 - Typically presents in adulthood
 - May not decrease life expectancy

Genetics

Gene: *CFTR*

Inheritance: autosomal recessive

Penetrance

- Severe pathogenic variants: high
- Mild pathogenic variants: variable

Variants

- >2,000 variants in *CFTR* gene
 - Most are very rare and not well characterized
 - 2.6% are large insertions/deletions
 - *CFTR* is the only gene known to be causative for CF
- BAVD
 - At least one pathogenic *CFTR* variant: ~75%
 - Two pathogenic *CFTR* variants: ~20%
 - One pathogenic *CFTR* variant and one 5T variant: 25%
 - One pathogenic *CFTR* variant: 20%
 - One 5T variant: 10%
- Idiopathic pancreatitis
 - Up to 40% are predicted to have at least one pathogenic *CFTR* variant

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity: 99%
 - Sequencing: 97% (Strom, 2003)
 - Deletion/duplication: 2.5% (Cystic Fibrosis Mutation Database, 2011)
- Analytical sensitivity/specificity
 - Sequencing: 99%
 - MLPA: 90%

Results

- Two severe pathogenic *CFTR* variants on opposite chromosomes
 - Predicted to be affected with classic CF
- One mild pathogenic non-CF-causing variant in combination with a CF-causing variant or another mild non-CF-causing variant on the opposite chromosome
 - Increased risk for a *CFTR*-related disorder such as pancreatitis, BAVD, and respiratory disease
- Only one severe variant
 - At least a CF carrier, but may be affected if a promoter or deep intronic variant is present that was not identified
- No pathogenic variants identified
 - Unlikely to be either affected with, or a carrier of, CF

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not detected
 - Breakpoints of large deletions/duplications
 - Regulatory region and deep intronic variants
- *CFTR* gene sequencing or deletion/duplication testing may identify variants of unknown clinical significance

References

- Abeliovich D, Lavon IP, Lerer I, et al. [Screening for five mutations detects 97% of cystic fibrosis \(CF\) chromosomes and predicts a carrier frequency of 1:29 in the Jewish Ashkenazi population](#). Am J Hum Genet. 1992;51(5):951-956. PubMed
- Bobadilla JL, Macek M Jr, Fine JP, et al. [Cystic fibrosis: a worldwide analysis of CFTR mutations--correlation with incidence data and application to screening](#). Hum Mutat. 2002;19(6):575-606. PubMed
- [Cystic Fibrosis Mutation Database](#). SickKids, Toronto, Canada. 2011.
- Heim RA, Sugarman EA, Allitto BA. [Improved detection of cystic fibrosis mutations in the heterogeneous U.S. population using an expanded, pan-ethnic mutation panel](#). Genet Med. 2001;3(3):168-176. PubMed
- Moskowitz SM, Chmiel JF, Sternen DL, et al. [Clinical practice and genetic counseling for cystic fibrosis and CFTR-related disorders](#). Genet Med. 2008;10(12):851-868. PubMed
- Strom CM, Huang D, Chen C, et al. [Extensive sequencing of the cystic fibrosis transmembrane regulator gene: assay validation and unexpected benefits of developing a comprehensive test](#). Genet Med. 2003;5(1):9-14. PubMed
- Sugarman EA, Rohlf EM, Silverman LM, et al. [CFTR mutation distribution among U.S. Hispanic and African American individuals: evaluation in cystic fibrosis patient and carrier screening populations](#). Genet Med. 2004;6(5):392-399. PubMed
- [ACOG Committee Opinion No. 486: Update on carrier screening for cystic fibrosis](#). Obstet Gynecol. 2011;117(4):1028-1031.
- Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med. 2004;6(5):387-931.

CFTR 165 Pathogenic Variants Tested		
Legacy Name	cDNA Name	Protein Name
M1V	c.1A>G	p.Met1Val
CFTRdele2,3 (deletion of exons 2 and 3)	c.54-5940_273+10250del	Exons 2-3del
Q39X	c.115C>T	p.Gln39X
E60X	c.178G>T	p.Glu60X
P67L	c.200C>T	p.Pro67Leu
R75X	c.223C>T	p.Arg75X
➤ G85E	c.254G>A	p.Gly85Glu
394delTT	c.262_263delTT	p.Leu88IlefsX22 aka p.Leu88fs
405+1G>A	c.273+1G>A	Intronic
405+3A>C	C.273+3A>C	Intronic
406-1G>A	c.274-1G>A	Intronic
E92K	c.274G>A	p.Glu92Lys
E92X	c.274G>T	p.Glu92X
Q98X	c.292C>T	p.Gln98X
444delA	c.313delA	p.Ile105SerfsX2 aka p.Ile105fs
457TAT>G	c.325_327delTATinsG	p.Tyr109GlyfsX4 aka p.Tyr109fs
D110H	c.328G>C	p.Asp110His
R117C	c.349C>T	p.Arg117Cys
➤ R117H	c.350G>A	p.Arg117His
Y122X	c.366T>A	p.Tyr122X
574delA	c.442delA	p.Ile148LeufsX5 aka p.Ile148fs
➤ 621+1G>T	c.489+1G>T	Intronic
663delT	c.531delT	p.Ile177MetfsX12 aka p.Ile177fs
G178R	c.532G>A	p.Gly178Arg
➤ 711+1G>T	c.579+1G>T	Intronic
711+5G>A	c.579+5G>A	Intronic
711+3A>G	c.579+3A>G	Intronic
712-1G>T	c.580-1G>T	Intronic
H199Y	c.595C>T	p.His199Tyr
P205S	c.613C>T	p.Pro205Ser
L206W	c.617T>G	p.Leu206Trp
Q220X	c.658C>T	p.Gln220X
L227R	c.680T>G	p.Leu227Arg
852del22	c.720_741delAGGGAGAATGATGATGAAGTAC	p.Gly241GlufsX13 aka p.Gly241fs
935delA	c.803delA	p.Asn268IlefsX17 aka p.Asn268fs
936delTA	c.805_806delAT	p.Ile269ProfsX4 aka p.Ile269fs
F311del	c.933_935delCTT	p.Phe312del
1078delT	c.948delT	p.Phe316LeufsX12 aka p.Phe316fs
G330X	c.988G>T	p.Gly330X
➤ R334W	c.1000C>T	p.Arg334Trp

CFTR 165 Pathogenic Variants Tested		
Legacy Name	cDNA Name	Protein Name
I336K	c.1007T>A	p.Ile336Lys
S341P	c.1021T>C	p.Ser341Pro
1154insTC	c.1022_1023insTC	p.Phe342HisfsX28 aka p.Phe342fs
R347H	c.1040G>A	p.Arg347His
➤ R347P	c.1040G>C	p.Arg347Pro
R352Q	c.1055G>A	p.Arg352Gln
1213delT	c.1081delT	p.Trp361GlyfsX8 aka p.Trp361fs
1248+1G>A	c.1116+1G>A	Intronic
1259insA	c.1127_1128insA	p.Gln378AlafsX4 aka p.Gln378fs
1288insTA	c.1153_1154insAT	p.Asn386IlefsX3 aka p.Asn386fs
W401X(TAG)	c.1202G>A	p.Trp401X
W401X(TGA)	c.1203G>A	p.Trp401X
1341+1G>A	c.1209+1G>A	Intronic
IVS8 5T ^a	c.1210-12 ⁵	Intronic
1461ins4	c.1329_1330insAGAT	p.Ile444ArgfsX3 aka p.Ile444fs
1471delA	c.1340delA	p.Lys447ArgfsX2 aka p.Lys447fs
➤ A455E	c.1364C>A	p.Ala455Glu
1525-1G>A	c.1393-1G>A	Intronic
S466X(TAA)	c.1397C>A	p.Ser466X
S466X(TAG)	c.1397C>G	p.Ser466X
L467P	c.1400T>C	p.Leu467Pro
1548delG	c.1418delG	p.Gly473GluX54 aka p.Gly473fs
G480C	c.1438G>T	p.Gly480Cys
S489X	c.1466C>A	p.Ser489X
S492F	c.1475C>T	p.Ser492Phe
Q493X	c.1477C>T	p.Gln493X
➤ I507del	c.1519_1521delATC	p.Ile507del
➤ F508del	c.1521_1523delCTT	p.Phe508del
1677delTA	c.1545_1546delTA	p.Tyr515X
V520F	c.1558G>T	p.Val520Phe
C524X	c.1572C>A	p.Cys524X
Q525X	c.1573C>T	p.Gln525X
➤ 1717-1G>A	c.1585-1G>A	Intronic
1717-8G>A	c.1585-8G>A	Intronic
➤ G542X	c.1624G>T	p.Gly542X
S549R(A>C)	c.1645A>C	p.Ser549Arg
S549N	c.1646G>A	p.Ser549Asn
S549R(T>G)	c.1647T>G	p.Ser549Arg
G551S	c.1651G>A	p.Gly551Ser
➤ G551D	c.1652G>A	p.Gly551Asp
Q552X	c.1654C>T	p.Gln552X

CFTR 165 Pathogenic Variants Tested		
Legacy Name	cDNA Name	Protein Name
➤ R553X	c.1657C>T	p.Arg553X
A559T	c.1675G>A	p.Ala559Thr
R560K	c.1679G>A	p.Arg560Lys
➤ R560T	c.1679G>C	p.Arg560Thr
1811+1.6kbA>G	c.1679+1.6kbA>G aka c.1679+1.6kbAG	Intronic
1812-1G>A	c.1680-1G>A	Intronic
1833delT	c.1703delT	p.Leu568CysfsX4 aka p.Leu568fs
Y569D	c.1705T>G	p.Tyr569Asp
P574H	c.1721C>A	p.Pro574His
E585X	c.1753G>T	p.Glu585X
➤ 1898+1G>A	c.1766+1G>A	Intronic
1898+3A>G	c.1766+3A>G	Intronic
1924del7	c.1792_1798delAAAACTA	p.Lys598GlyfsX11 aka p.Lys598fs
2043delG	c.1911delG	p.Gln637HisfsX26 aka p.Gln637fs
2055del9>A	c.1923_1931del9insA	p.Ser641ArgfsX5 aka p.Ser641fs
2105-2117del13insAGAAA	c.1973_1985del13insAGAAA	p.Arg658LysfsX4 aka p.Arg658fs
2108delA	c.1976delA	p.Asn659IlefsX4 aka p.Asn659fs
2143delT	c.2012delT	p.Leu671X
2183delAA	c.2051_2052del	p.Lys684ThrfsX4
2183AA>G	c.2051_2052delinsG aka c.2051_2delinsG	p.Lys684SerfsX38
➤ 2184delA	c.2052delA	p.Lys684AsnfsX38
R709X	c.2125C>T	p.Arg709X
K710X	c.2128A>T	p.Lys710X
2307insA	c.2175_2176insA	p.Glu726ArgfsX4 aka p.Glu726fs
L732X	c.2195T>G	p.Leu732X
2347delG	c.2215delG	p.Val739TyrfsX16 aka p.Val739fs
R764X	c.2290C>T	p.Arg764Ter
2585delT	c.2453delT	p.Leu818TrpfsX3 aka p.Leu818fs
E822X	c.2464G>T	p.Glu822X
2622+1G>A	c.2490+1G>A	Intronic
E831X	c.2491G>T	p.Glu831X
W846X	c.2537G>A	p.Trp846X
W846X(2670TGG>TGA)	c.2538G>A	p.Trp846X
R851X	c.2551C>T	p.Arg851X
2711delT	c.2583delT	p.Phe861LeufsX3 aka p.Phe861fs
➤ 2789+5G>A	c.2657+5G>A	Intronic
Q890X	c.2668C>T	p.Gln890X
2869insG	c.2737_2738insG	p.Tyr913X

CFTR 165 Pathogenic Variants Tested		
Legacy Name	cDNA Name	Protein Name
L927P	c.2780T>C	p.Leu927Pro
2942insT	c.2810_2811insT	p.Val938GlyfsX37 aka p.Val938fs
S945L	c.2834C>T	p.Ser945Leu
3007delG	c.2875delG	p.Ala959HisfsX9 aka p.Ala959fs
G970R	c.2908G>C	p.Gly970Arg
➤ 3120+1G>A	c.2988+1G>A	Intronic
3120G>A	c.2988G>A	Intronic
3121-1G>A	c.2989-1G>A	Intronic
3171delC	c.3039delC	p.Tyr1014ThrfsX9 aka p.Tyr1014fs
3199del6	c.3067_3072delATAGTG	p.Ile1023_Val1024del aka I1023_V1024del
3272-26A>G	c.3140-26A>G	Intronic
L1065P	c.3194T>C	p.Leu1065Pro
R1066C	c.3196C>T	p.Arg1066Cys
R1066H	c.3197G>A	p.Arg1066His
L1077P	c.3230T>C	p.Leu1077Pro
W1089X	c.3266G>A	p.Trp1089X
Y1092X(C>A)	c.3276C>A	p.Tyr1092X
Y1092X(C>G)	c.3276C>G	p.Tyr1092X
M1101K	c.3302T>A	p.Met1101Lys
E1104X	c.3310G>T	p.Glu1104X
R1158X	c.3472C>T	p.Arg1158X
➤ R1162X	c.3484C>T	p.Arg1162X
➤ 3659delC	c.3528delC	p.Lys1177SerfsX15 aka p.Lys1177fs
3667del4	c.3536_3539del	p.Thr1179AsnfsX12 aka p.Thr1179fs
S1196X	c.3587C>G	p.Ser1196X
W1204X(3743G>A)	c.3611G>A	p.Trp1204X
W1204X(3744G>A)	c.3612G>A	p.Trp1204X
3791delC	c.3659delC	p.Thr1220LysfsX8 aka p.Thr1220fs
3821delT	c.3691delT	p.Ser1231ProfsX4 aka p.Ser1231fs
Q1238X	c.3712C>T	p.Gln1238X
➤ 3849+10kbC>T	c.3718-2477C>T	Intronic
G1244E	c.3731G>A	p.Gly1244Glu
3876delA	c.3744delA	p.Lys1250ArgfsX9 aka p.Lys1250fs
S1251N	c.3752G>A	p.Ser1251Asn
S1255P	c.3763T>C	p.Ser1255Pro
S1255X	c.3764C>A	p.Ser1255X
3905insT	c.3773_3774insT	p.Leu1258PhefsX7 aka p.Leu1258fs
➤ W1282X	c.3846G>A	p.Trp1282X

CFTR 165 Pathogenic Variants Tested		
Legacy Name	cDNA Name	Protein Name
4005+1G>A	c.3873+1G>A	Intronic
➤ N1303K	c.3909C>G	p.Asn1303Lys
Q1313X	c.3937C>T	p.Gln1313X
CFTRdele22,23	c.3964-78_4242+577del	Exons 22-23del
G1343Afs	c.4028delG	p.Gly1343AlafsX4 aka p.Gly1343fs
G1349D	c.4046G>A	p.Gly1349Asp
4209TGTT>AA	c.4077_4080delTGTTinsAA	p.Val1360delfsX3 aka p.Val1360fs
E1371X	c.4111G>T	p.Glu1371X
4382delA	c.4251delA	p.Glu1418ArgfsX14 aka p.Glu1418fs
➤ 23 variants recommended for carrier screening by ACMG/ACOG *The IVS8 5T variant, c.1210-12 ⁵ , will be reported when R117H is detected and in individuals who are reported to be symptomatic		