Cystic Fibrosis (CFTR) Expanded Variant Panel

Last Literature Review: April 2022 Last Update: August 2023

Cystic fibrosis (CF) is an autosomal recessive disorder caused by 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. Life expectancy is reduced. *CFTR*-related disorders are less severe and may be characterized by idiopathic pancreatitis, bilateral absence of the vas deferens, bronchiectasis, and/or nasal polyposis. These disorders typically present in adulthood and may not decrease life expectancy. Molecular testing may be used for carrier screening and diagnostic testing.

The American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) recommended carrier screening for 23 specific pathogenic *CFTR* variants in all couples planning a pregnancy or currently expecting.[1,2]

Featured ARUP Testing

Cystic Fibrosis (CFTR) Expanded Variant Panel 2013661

Method: Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) Mass Spectrometry

- Use for carrier screening for expectant individuals or couples planning a pregnancy
- Diagnostic testing for individuals with symptoms of classic CF

Cystic Fibrosis (CFTR) Expanded Variant Panel, Fetal 2013662

Method: Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) Mass Spectrometry/Fragment Analysis

- For use in individuals with suspected CF
- This test is not indicated for routine carrier screening

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

Incidence and Carrier Frequency of CF

Ethnicity	Incidence of Classic CF[1]	Carrier Frequency
Ashkenazi Jewish	1/2,300	1/24
Caucasian/White	1/2,500	1/25
Hispanic American	1/13,500	1/58
African American/Black	1/15,100	1/61
Asian American	1/35,100	1/94

Genetics

Gene

CFTR

Variants

There are over 2,000 identified variants in the *CFTR* gene, though most are very rare and not well characterized. *CFTR* is the only gene known to be causative for CF. Classic CF is caused by two severe pathogenic *CFTR* variants on opposite chromosomes. *CFTR*-related disorders are generally caused by one severe and one mild *CFTR* variant on opposite chromosomes.

For a full list of variants tested, see the Variants Tested table.

Inheritance

Autosomal recessive

Penetrance

- Complete for two severe variants on opposite chromosomes
- Incomplete when there are two pathogenic variants on opposite chromosomes and at least one is mild or a variant of varying clinical consequences (ie, one severe and one mild variant). Such combinations may or may not cause symptoms of a *CFTR*-related disorder.

Test Description

All variants in the Variants Tested table are assessed.

If one copy of the R117H variant is detected, then testing for the mild 5T variant is performed. If the 5T variant is also detected, cis/trans testing is performed to determine whether the variants are on the same chromosome. The mild 5T variant, c.1210−12[5], will only be reported if either the R117H variant is detected or the individual is reported to be symptomatic.

Test Interpretation

Result	Interpretation	Recommendations
No *CFTR* variants identified	Reduced risk for being a carrier of or affected with CF	See risk reduction in the Carrier Risk for Asymptomatic Individuals and Percentage of Patients With CF tables
One severe *CFTR* variant identified	At least a carrier of CF and may be affected if an additional variant is present but not identified	Consider sequencing and deletion/duplication analysis if symptomatic Offer carrier screening to relatives and reproductive partner
Two severe *CFTR* variants identified	Predicted to be affected	Refer to a CF clinic for disease management Offer carrier screening to family members and reproductive partner
Two *CFTR* variants detected (at least one of which is mild)	Increased risk for a *CFTR*-related disorder	If one of the CF variants identified is severe, CF carrier screening should be offered to family members and reproductive partner

Sensitivity/Specificity

Clinical Sensitivity

Clinical sensitivity varies depending on ethnicity.

Carrier Risk for Asymptomatic Individuals Before and After a Negative Cystic Fibrosis (*CFTR*) Expanded Variant Panel			
Ethnicity	**Variant Detection Rate**	**Carrier Risk Before Test**	**Carrier Risk After Negative Test**
African American/Black	78%	1/61	1/275
Ashkenazi Jewish	96%	1/24	1/575
Asian American	55%	1/94	1/210
Hispanic American	80%	1/58	1/285
Caucasian	92%	1/25	1/300

Percentage of Patients With CF Who Have None or Only One Detectable Variant on Cystic Fibrosis (*CFTR*) Expanded Variant Panel		
Ethnicity	**CF Patients With No Detectable Pathogenic Variants**	**CF Patients With Only One Detectable Pathogenic Variant**

Ethnicity	CF Patients With No Detectable Pathogenic Variants	CF Patients With Only One Detectable Pathogenic Variant
African American/Black	5%	34%
Ashkenazi Jewish	1%	7%
Asian American	20%	50%
Hispanic American	4%	32%
Caucasian	1%	15%

Analytic Sensitivity/Specificity

99%

Limitations

- Diagnostic errors can occur due to rare sequence variations.
- Only *CFTR* variants listed in the Variants Tested table will be interrogated.

Variants Tested

CFTR Variants Tested by Cystic Fibrosis (*CFTR*) Expanded Variant Panel		
Legacy Name	**cDNA Name**	**Protein Name**
M1V	c.1A>G	p.Met1Val
CFTRdele2,3 (deletion of exons 2 and 3)	c.54-5940_273+10250del21kb	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

♦ 23 variants recommended for carrier screening by ACMG/ACOG.

[a]The IVS8 5T variant, c.1210-125, will be reported when R117H is detected and in individuals who are reported to be symptomatic

Legacy Name	cDNA Name	Protein Name
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

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Legacy Name	cDNA Name	Protein Name
852del22	c.722_743del	p.Gly241GlufsX13 aka p.Gly241fs
935delA	c.803delA	p.Asn268IlefsX17 aka p.Asn268fs
936delTA	c.805_806delAT	p.Ile269ProfsX4 aka p.Ile269fs
F312del	c.935_937delTCT	p.Phe312del
1078delT	c.948delT	p.Phe316LeufsX12 aka p.Phe316fs
G330X	c.988G>T	p.Gly330X
♦ R334W	c.1000C>T	p.Arg334Trp
I336K	c.1007T>A	p.Ile336Lys
S341P	c.1021T>C	p.Ser341Pro
1154insTC	c.1021_1022dupTC	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.1130dupA	p.Gln378AlafsX4 aka p.Gln378fs
1288insTA	c.1155_1156dupTA	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

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Legacy Name	cDNA Name	Protein Name
IVS8 5Ta	c.1210−125	Intronic
1461ins4	c.1327_1330dupGATA	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.Gly473GlufsX54 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**

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Legacy Name	cDNA Name	Protein Name
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
♦ 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.1680-886A>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

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Legacy Name	cDNA Name	Protein Name
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.2175dupA	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

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Legacy Name	cDNA Name	Protein Name
♦ 2789+5G>A	**c.2657+5G>A**	**Intronic**
Q890X	c.2668C>T	p.Gln890X
2869insG	c.2737_2738insG	p.Tyr913X
L927P	c.2780T>C	p.Leu927Pro
2942insT	c.2810dupT	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

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Legacy Name	cDNA Name	Protein Name
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**
3667ins4	c.3532_3535dupTCAA	p.Thr1179IlefsX17 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.3773dupT	p.Leu1258PhefsX7 aka p.Leu1258fs
♦ W1282X	**c.3846G>A**	**p.Trp1282X**
4005+1G>A	c.3873+1G>A	Intronic
♦ N1303K	**c.3909C>G**	**p.Asn1303Lys**

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Legacy Name	cDNA Name	Protein Name
Q1313X	c.3937C>T	p.Gln1313X
CFTRdele22,23	c.3964-78_4242+577del	Exons 22-23del
C1344fs	c.4025_4028dup	p.Cys1344GlyfsX16 aka p.C1344fs
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

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References

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2. ACOG Committee Opinion No. 486: Update on carrier screening for cystic fibrosis. *Obstet Gynecol*. 2011;117(4):1028-1031.

Additional Resources

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Related Information

Cystic Fibrosis
Cystic Fibrosis (CFTR) Sequencing and Deletion/Duplication
Fragile X (FMR1) With Reflex to Methylation Analysis
Spinal Muscular Atrophy Copy Number Analysis