Cystic Fibrosis (CFTR) Expanded Variant Panel

Last Literature Review: January 2025 Last Update: May 2025

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) recommend *CTFR* carrier screening for all couples planning a pregnancy or currently expecting.[1,2]

ACMG now recommends carrier screening for 100 specific, pathogenic CFTR variants, an increase from the previously recommended 23 variants (known as "ACMG-23").[2] The Cystic Fibrosis (CFTR) Expanded Variant Panel detects 165 variants, which include the previously established 23 pathogenic CFTR variants and 69 of the 100 ACMG-recommended variants. Refer to the Variants Tested section for a complete list.

Disease Overview

Incidence and Carrier Frequency of CF

Ethnicity	Incidence of Classic CF[3]	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 more than 2,000 identified variants in the *CFTR* gene, although 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 consequence (i.e., 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
1 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
2 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
2 *CFTR* variants detected (at least 1 mild)	Increased risk for a *CFTR*-related disorder	If severe CF variant is identified, 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/White	92%	1/25	1/300

Percentage of Patients With CF Who Have No 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
African American/Black	5%	34%
Ashkenazi Jewish	1%	7%
Asian American	20%	50%
Hispanic American	4%	32%

Ethnicity	CF Patients With No Detectable Pathogenic Variants	CF Patients With Only One Detectable Pathogenic Variant
Caucasian/White	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**
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

Legacy Name	cDNA Name	Protein Name
♦ 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.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

Legacy Name	cDNA Name	Protein Name
		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
IVS8 5T[a]	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**
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**

Legacy Name	cDNA Name	Protein Name
♦ 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
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**

Legacy Name	cDNA Name	Protein Name
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
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**	**p.Gln996=**
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

Legacy Name	cDNA Name	Protein Name
♦ 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.Arg1162**X
♦ 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**
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

Legacy Name	cDNA Name	Protein Name
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

♦ Panel includes 69/100 variants recommended for carrier screening by ACMG.

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

Source: Deignan 2023[2]

References

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

2. Deignan JL, Gregg AR, Grody WW, et al. Updated recommendations for CFTR carrier screening: a position statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2023;25(8):100867.

3. 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):387-391.

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com