Supplementary Information for v410, 094

Table 1: Cl^- channel properties and averaged macroscopic Cl^- and HCO_3^- transport mediated by WT CFTR and CFTR mutants.

Mutation	CFTR Domain	[a]Channel NPo (%)	[a]Macroscopic Current (%)	Cl^- transport mM/sec (n)	HCO_3 transport pH units/min (n)	[b]Pancreatic Status (References)
WT		100	100	0.36±0.04(6)	0.87±0.05(8)	
R117H	EL1/TM2	28	15	0.11±0.02(3)*	0.53±0.04(3)	PS (7)
I148T	CL1	100	100	0.36±0.03(4)	0.07±0.03 (4)	PI (8)
G178R	CL1	75	50	0.35±0.03(4)	0.05±0.02(5)	PI (9)
E193K	CL1	25	100	0.33±0.02(5)	0.29±0.03(4)	PS (10)
ΔF508	NBD1	-	-	[c]0.00 (4)	[c]0.00 (7)	PI (7)
G551D	NBD1	15	25 or 60	0.19±0.03(4)*	0.00(5)	PI (11)
G551S	NBD1	Abnormal gating	100	0.41±0.02(4)	0.36±0.02(5)	PS (12)
H620Q	RD	150	250	0.82±0.08(3)*	0.12±0.05(4)	PI (13)
D648V	RD	-	90	0.50±0.05(4)*	0.55±0.06(4)	PS (14)
A800G	RD	180	350	0.91±0.09(4)*	0.67±0.07(3)	PS (10)
H949Y	CL3	200	100	0.35±0.03(3)	0.37±0.05(4)	PS (15)
G970R	CL3	30	-	0.27±0.03(3)	0.02±0.01(3)	[d]PI
A1067T	CL4	50	50	0.49±0.06(5)*	0.06±0.02(4)	PI (16)
R1070Q	CL4	50	50	0.37±0.04(4)	0.41±0.03(5)	PI/PS (17)
G1244E	NBD2	Abnormal gating	100	0.36±0.04(5)	0.00(5)	PI (18)
S1255P	NBD2	Abnormal gating	100	0.42±0.03(3)	0.01±0.01(5)	PI (19)
G1349D	NBD2	Abnormal gating	100	0.36±0.03(6)	0.00(10)	PI (20)

Indicates different from WT CFTR, $p<0.05$; [a]Cl^- channel properties were taken from reference 1-6 below and [b]pancreatic status of patients carrying the indicated CFTR mutations were taken from the references 7-20 below as listed in parenthesis next to the phenotypes. [c]Results were taken from reference 12. [d]Harry Cuppens, personal communication. Results are given as the Mean±S.E.M of the number of experiments indicated in parenthesis.

References

1. Seibert FS, et al, Disease-associated mutations in cytoplasmic loops 1 and 2 cystic fibrosis transmembrane conductance regulator impede processing or opening of the channel. Biochemistry 36, 11966-11974, (1997).
2. Illek B, et al, Defective function of the cystic fibrosis-causing missense mutation G551D is recovered by genistein. Am J Physiol 277, C833-C839, (1999).
3. Anderson M, Welsh MJ, Regulation by ATP and ADP of CFTR chloride channels that contain mutant nucleotide-binding domains. Science 257,1701-1704, (1992).

4. Vankeerberghen A et al, Characterization of 19 disease-associated missense mutations in the regulatory domain of the cystic fibrosis transmembrane conductance regulator. Human Molecular Genetics 7, 1761-1769 (1998).
5. Seibert FS. et al, Cytoplasmic loop three of cystic fibrosis transmembrane conductance regulator contributes to regulation of chloride channel activity. J Biol Chem 271, 27493-27499, (1996).
6. Seibert FS, et al, Disease-associated mutations in the fourth cytoplasmic loop of cystic fibrosis transmembrane conductance regulator compromise biosynthetic processing and chloride channel activity. J Biol Chem 271 ,15139-15145 (1996).
7. Kristidis P, et al, Genetic determination of exocrine pancreatic function in cystic fibrosis. *Am J Hum Genet* 50, 1178-1184 (1992).
8. Bozon D, Zielenski J, Rininsland F, Tsui LC, Identification of four new mutations in the cystic fibrosis transmembrane conductance regulator gene: I148T, L1077P, Y1092X, 2183AA-->G. Human mutation 3, 330-332, (1994).
9. Zielenski J et al, Identification of mutations in exons 1 through 8 of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Genomics 10, 229-235, (1991).
10. Mercier B, et al, Is congenital bilateral absence of vas deferens a primary form of cystic fibrosis? Analyses of the CFTR gene in 67 patients. Am J Hum Genet 56, 272-277, (1995).
11. Hughes DJ, et al. Mutation characterization of CFTR gene in 206 Northern Irish CF families: thirty mutations, including two novel, account for approximately 94% of CF chromosomes. Hum Mutat. 8:340-347, (1996).
12. Strong TV, et al, Cystic fibrosis gene mutation in two sisters with mild disease and normal sweat electrolyte levels. New Eng. J Med 325, 1630-1634, (1991).
13. Vankeerberghen A et al, Characterization of 19 disease-associated missense mutations in the regulatory domain of the cystic fibrosis transmembrane conductance regulator. Human Molecular Genetics 7, 1761-1769 (1998).
14. Mercier B, et al, Complete detection of mutations in cystic fibrosis patients of Native American origin. Hum Genet 94, 629-632, (1994).
15. Ghanem N, et al, Identification of eight mutations and three sequence variations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Genomics 21, 434-436, (1994).
16. Ferec C, et al, Detection of over 98% cystic fibrosis mutations in a Celtic population. Nat Genet 1, 188-191, (1992).
17. Mercier B et al, Identification of eight novel mutations in a collaborative analysis of a part of the second transmembrane domain of the CFTR gene. Genomics 16, 296-297, (1993).
18. Devoto M et al, Screening for non-delta F508 mutations in five exons of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in Italy. Am J Hum Genet 48, 1127-1132, (1991).
19. Lissens W, Bonduelle M, Malfroot A, Dab I, Liebaers I. A serine to proline substitution (S1255P) in the second nucleotide binding fold of the cystic fibrosis gene. Human Mol. Genetics 1, 441- 442, (1992).
20. Gregory RJ et al, Maturation and function of cystic fibrosis transmembrane conductance regulator variants bearing mutations in putative nucleotide-binding domains 1 and 2. Mol. Cellular. Biol. 11, 3886-3893, (1991).