Supplementary Table S2: Grouped variant testing in COPDGene using SKAT-O

	CF-causing		**CF-causing + Varying clinical consequence**		**CF-causing + Varying clinical consequence + Predicted functional**	**All coding variants**
# of Variants	36 (33 variants in weighted analysis)		61 (58 variants in weighted analysis)		206	297[1]
# of Alleles	254		548		866	2820
	p-value	**p-value with weighting[2]**	**p-value**	**p-value with weighting[2]**	**p-value**	**p-value**
Chronic Bronchitis	0.016	0.015	0.055	0.015	0.056	0.15
COPD	0.049	0.044	0.14	0.045	0.12	0.088
Severe COPD	0.37	0.34	0.42	0.35	0.20	0.029
Severe Exacerbations	0.18	0.17	0.38	0.18	0.31	0.30
BMI	0.22	0.20	0.40	0.21	0.42	0.30
FEV1 percent predicted	0.25	0.22	0.18	0.22	0.15	0.23
Percent Emphysema	0.37	0.38	0.42	0.38	0.44	0.20
Airway Wall Thickness	0.11	0.11	0.019	0.098	0.024	0.028
Bronchodilator Response % FEV1[1]	0.023	0.020	0.025	0.020	0.020	0.21

1. All -p-values are one-sided except for BDR which is two sided
2. SKAT was performed with weighting for %pancreatic insufficiency as a measure of disease severity. Three variants did not have pancreatic insufficiency data and were therefore excluded from the weighted analysis

Supplementary Table S3: Burden testing in COPDGene stratified by current smoking status. P-values and effect sizes for variant-set testing of *CFTR* variants with chronic bronchitis.

	Current Smokers			**Former Smokers**		
	Chronic Bronchitis		p-value/ OR*	Chronic Bronchitis		p-value/ OR*
	Yes	No		Yes	No	
CF-causing	45 (39.5%)	69	0.0082 *(OR=1.62)*	23 (17.2%)	111	0.082
CF-causing + Varying clinical consequence	76 (31.7%)	164	0.037 *(OR=1.22)*	33 (15.3%)	182	0.31
CF-causing + Varying clinical consequence + Predicted functional	115 (29.8%)	271	0.011 *(OR=1.24)*	54 (15.6%)	292	0.23
All coding variants	313 (26.8%)	856	0.45	150 (13.2%)	988	0.46
Controls (no CFTR variants)	813 (23.9%)	2579	-	389 (13.5%)	2500	-

*All -p-values are one-sided. Odds ratios or beta coefficients are shown for all nominally significant associations ($p<0.05$).

Supplementary Table S4: Burden testing in COPDGene stratified by COPD case control status. P-values and effect sizes for variant-set testing of *CFTR* variants with chronic bronchitis.

	COPD Cases			**Smoking Controls**		
	Chronic Bronchitis		p-value/ OR*	Chronic Bronchitis		p-value/ OR*
	Yes	No		Yes	No	
CF-causing	51 (38.1%)	83	0.0022 *(OR=1.72)*	17 (14.9%)	97	0.37
CF-causing + Varying clinical consequence	72 (33.8%)	141	0.038 *(OR=1.27)*	37 (15.4%)	203	0.23
CF-causing + Varying clinical consequence + Predicted functional	106 (31.5%)	231	0.022 *(OR=1.24)*	62 (15.9%)	327	0.13
All coding variants	308 (28.1%)	787	0.16	150 (12.5%)	1047	0.11
Controls (no CFTR variants)	701 (25.5%)	2050	-	493 (14.1%)	2996	-

*All -p-values are one-sided. Odds ratios or beta coefficients are shown for all nominally significant associations ($p<0.05$).

Supplementary Table S5: Single variant testing of all variants in COPDGene with severe COPD. Variants with minor allele count > 10 were included in this analysis.

Variant ID	HGVS ID (legacy name)	Allele counts	Severe COPD		Effect	CFTR2 Determination	SNFEff function
			One sided p-value (Effect Size)	One sided p-value with permutation			
rs142540482	c.221G>A (R74Q)	11	0.0038 *(OR=7.30)*	0.16	Missense variant	Reported in CFTR2; not yet annotated	MODERATE
chr7:117509093:G:A	c.224G>A (R75Q)	459	0.0068 *(OR=1.38)*	0.02	Missense variant	Non CF-causing	MODERATE
rs150157202	c.2260G>A (V754M)	28	0.015 *(OR=2.76)*	0.09	Missense variant	Non CF-causing	MODERATE
rs143486492	c.890G>A (R297Q)	17	0.050	0.17	Missense variant	Reported in CFTR2; not yet annotated	MODERATE
chr7:117530975:G:A	c.350G>A (R117H)	27	0.062	0.16	Missense variant	Varying clinical consequence	MODERATE
rs151073129	c.853A>T (I285F)	21	0.081	0.14	Missense variant	Reported in CFTR2; not yet annotated	MODERATE
chr7:117548796:G:A	c.1365G>A	21	0.081	0.15	Synonymous variant	Not reported in CFTR2	LOW
chr7:117666903:C:T	c.4243-5C>T (4375-5C->T)	23	0.11	0.16	Splice region variant & intron variant	Reported in CFTR2; not yet annotated	LOW
chr7:117559594:T:G	c.1523T>G (F508C)	19	0.11	0.23	Missense variant	Non CF-causing	MODERATE
rs34911792	c.3705T>G (S1235R)	131	0.13	0.13	Missense variant	Non CF-causing	MODERATE
rs1800094	c.1581A>G	78	0.15	0.14	Synonymous variant	Not reported in CFTR2	LOW
rs60887846	c.2820T>G	25	0.26	0.07	Synonymous variant	Not reported in CFTR2	LOW

rs1800118	c.3285A>T	109	0.30	0.35	Synonymous variant	Reported in CFTR2; not yet annotated	LOW
rs1800103	c.2421A>G (I807M)	10	0.31	0.21	Missense variant	Non CF-causing	MODERATE
rs371315549	c.274-6T>C (406-6T->C)	13	0.42	0.28	Splice region variant & intron variant	Reported in CFTR2; not yet annotated	LOW
rs1800111	c.2991G>C (L997F)	29	0.45	0.45	Missense variant & splice region variant	Non CF-causing	MODERATE
chr7:117531068:T:C	c.443T>C (I148T)	22	0.50	0.63	Missense variant	Non CF-causing	MODERATE
chr7:117559655:G:A	c.1584G>A (1716G/A)	290	0.51	0.54	Splice region variant & synonymous variant	Non CF-causing	LOW
rs1800112	c.3080T>C (I1027T)	11	0.57	0.53	Missense variant	Non CF-causing	MODERATE
rs199826652	c.1521_1523 delCTT (F508del)	177	0.62	0.68	Disruptive inframe deletion	CF-causing	MODERATE
chr7:117642528:G:A	c.3808G>A (D1270N)	86	0.65	0.57	Missense variant	Varying clinical consequence	MODERATE
rs75541969	c.3454G>C (D1152H)	14	0.68	0.66	Missense variant	Varying clinical consequence	MODERATE
chr7:117504290:C:T	c.91C>T (R31C)	28	0.69	0.70	Missense variant	Non CF-causing	MODERATE
rs140455771	c.2249C>T (P750L)	14	0.74	0.73	Missense variant	Varying clinical consequence	MODERATE
rs1800110	c.2900T>C (L967S)	29	0.76	0.69	Missense variant	Varying clinical consequence	MODERATE
rs1800109	c.2898G>A (3030G/A)	166	0.78	0.76	Synonymous variant	Reported in CFTR2; not yet annotated	LOW
rs1800100	c.2002C>T (R668C)	105	0.84	0.82	Missense variant	Non CF-causing	MODERATE
rs115545701	c.220C>T (R74W)	82	0.85	0.81	Missense variant	Varying clinical consequence	MODERATE

rs151235408	c.2245C>T (2377C/T)	14	0.86	0.84	Synonymous variant	Reported in CFTR2; not yet annotated	LOW
chr7:117590400:G:C	c.1727G>C (G576A)	85	0.88	0.93	Missense variant	Non CF-causing	MODERATE
chr7:117627538:G:T	c.3485G>T (R1162L)	17	0.93	0.05	Missense variant	Non CF-causing	MODERATE
rs1800079	c.509G>A (R170H)	12	0.94	0.13	Missense variant	Non CF-causing	MODERATE
rs148783445	c.4333G>A (D1445N)	11	0.95	0.12	Missense variant	Reported in CFTR2; not yet annotated	MODERATE
rs1800135	c.4272C>T (4404C/T)	136	0.97	0.98	Synonymous variant	Reported in CFTR2; not yet annotated	LOW
rs1800131	c.3897A>G (4029A/G)	17	0.98	0.97	Synonymous variant	Reported in CFTR2; not yet annotated	LOW
chr7:117603609:C:T	c.2735C>T (S912L)	16	1.00	0.94	Missense variant	Unknown significance	MODERATE

Supplementary Table S6: CFTR Compound Heterozygous Subjects in COPDGene

Variant 1/ Variant 2 HGVSc	Variant Determination	Case/ Control	Current Smoker Status	Chronic Bronchitis	Bronchiectasis
c.1521_1523delCTT c.1584G>A	CF-causing/ Non CF causing	Control	Current	No	
c.1521_1523delCTT c.1584G>A	CF-causing/ Non CF-causing	Control	Former	No	
c.1521_1523delCTT c.1584G>A	CF-causing/ Non CF-causing	Case	Former	Chronic Bronchitis	Bronchiectasis score=2; 2 lobes with bronchiectasis
c.1521_1523delCTT c.1584G>A	CF-causing/ Non CF-causing	Case	Former	No	
c.1521_1523delCTT c.2735C>T	CF-causing/ MODERATE	Control	Former	No	
c.1521_1523delCTT c.3485G>T	CF-causing/ Non CF-causing	Case	Former	No	
c.1521_1523delCTT c.650A>G	CF-causing/ MODERATE	Case	Former	No	
c.1521_1523delCTT / c.221G>A and c.890G>A[1]	CF-causing/ MODERATE	Case	Current	Chronic Bronchitis	
c.1521_1523delCTT c.221G>A and c.890G>A	CF-causing/ MODERATE	Case	Current	Chronic Bronchitis	
c.1521_1523delCTT c.2855T>C	CF-causing/ MODERATE	Control	Former	No	
c.1521_1523delCTT c.2245C>T	CF-causing/ LOW	Case	Current	Chronic Bronchitis	
c.1521_1523delCTT c.2002C>T	CF-causing/ MODERATE	Case	Former	No	
c.1521_1523delCTT c.2002C>T	CF-causing/ MODERATE	Case	Former	Chronic Bronchitis	No bronchiectasis
c.1521_1523delCTT	CF-causing/	Case	Former	No	

c.2900T>C	Varying clinical consequence				
c.1521_1523delCTT c.3285A>T	CF-causing/ LOW	Case	Current	No	
c.1521_1523delCTT c.4272C>T	CF-causing/ LOW	Case	Former	No	
c.1521_1523delCTT c.4272C>T	CF-causing/ LOW	Control	Current	Chronic Bronchitis	
c.1521_1523delCTT c.4272C>T	CF-causing/ LOW	Case	Current	Chronic Bronchitis	
c.1521_1523delCTT c.3705T>G	CF-causing/ Non CF-causing	Control	Former	No	Bronchiectasis score=5; 3 lobes with bronchiectasis
c.1521_1523delCTT c.3705T>G	CF-causing/ Non CF-causing	Case	Current	No	
c.1521_1523delCTT c.589T>C	CF-causing/ LOW	Case	Current	Chronic Bronchitis	
c.1521_1523delCTT c.224G>A	CF-causing/ Non CF-causing	Case	Former	No	
c.1521_1523delCTT c.224G>A	CF-causing/ Non CF-causing	Case	Former	Chronic Bronchitis	No bronchiectasis
c.1521_1523delCTT c.224G>A	CF-causing/ Non CF-causing	Case	Current	No	
c.1521_1523delCTT c.224G>A	CF-causing/ Non CF-causing	Case	Former	No	
c.1521_1523delCTT c.224G>A	CF-causing/ Non CF-causing	Control	Current	No	
c.1521_1523delCTT c.727A>G	CF-causing/ MODERATE	Control	Current	No	
c.3209G>A/ c.3808G>A	Varying clinical consequence/ Varying clinical consequence	Control	Current	No	
c.350G>A/ c.2900T>C and	Varying clinical consequence/	Case	Former	No	

c.3808G>A[2]	Varying clinical consequence				
c.1865G>A/ c.220C>T and c.3808G>A[3]	Varying clinical consequence/ Varying clinical consequence	Case	Former	No	
c.220C>T and c.3808G>A/ c.220C>T and c.3808G>A[3]	Varying clinical consequence/ Varying clinical consequence	Control	Current	No	
c.220C>T and c.3808G>A/ c.220C>T and c.3808G>A[3]	Varying clinical consequence/ Varying clinical consequence	Control	Former	No	Bronchiectasis score=6; 3 lobes with bronchiectasis

[1] c.890G>A is often in cis with c.221G>A. Both variants are missense variants predicted to have moderate impact on CFTR protein

[2] c.2900T>C was found in cis with c.3808G>A in one subject. Both variants have varying clinical consequence.

[3] c.2900T>C is often in cis with c.3808G>A. Both variants have varying clinical consequence

Supplementary Table S7: Alternative variants IDs for compound heterozygous subjects in COPDGene

Variant 1/ Variant 2 Variant ID	**Variant 1/ Variant 2 HGVSc ID**	**Variant 1/ Variant 2 Legacy Name**
rs199826652/ chr7:117559655:G:A	c.1521_1523delCTT/ c.1584G>A	F508del/ 1716G/A
rs199826652/ chr7:117559655:G:A	c.1521_1523delCTT/ c.1584G>A	F508del/ 1716G/A
rs199826652/ chr7:117559655:G:A	c.1521_1523delCTT/ c.1584G>A	F508del/ 1716G/A
rs199826652/ chr7:117559655:G:A	c.1521_1523delCTT/ c.1584G>A	F508del/ 1716G/A
rs199826652/ chr7:117603609:C:T	c.1521_1523delCTT/ c.2735C>T	F508del/ S912L
rs199826652/ chr7:117627538:G:T	c.1521_1523delCTT/ c.3485G>T	F508del
rs199826652/ rs121909046	c.1521_1523delCTT/c.650A>G	F508del/ E217G
rs199826652/ rs142540482 and rs143486492	c.1521_1523delCTT/ c.221G>A and c.890G>A	F508del/ R74Q and R297Q
rs199826652/ rs142540482 and rs143486492	c.1521_1523delCTT/ c.221G>A and c.890G>A	F508del/R74Q and R297Q
rs199826652/ rs142773283	c.1521_1523delCTT/ c.2855T>C	F508del/M952T
rs199826652/ rs151235408	c.1521_1523delCTT/ c.2245C>T	F508del/2377C/T
rs199826652/ rs1800100	c.1521_1523delCTT/ c.2002C>T	F508del
rs199826652/ rs1800100	c.1521_1523delCTT/ c.2002C>T	F508del
rs199826652/ rs1800110	c.1521_1523delCTT/ c.2900T>C	F508del/L967S
rs199826652/ rs1800118	c.1521_1523delCTT/ c.3285A>T	F508del
rs199826652/ rs1800135	c.1521_1523delCTT/ c.4272C>T	F508del/4404C/T
rs199826652/ rs1800135	c.1521_1523delCTT/ c.4272C>T	F508del/4404C/T
rs199826652/ rs1800135	c.1521_1523delCTT/ c.4272C>T	F508del/4404C/T
rs199826652/ rs34911792	c.1521_1523delCTT/ c.3705T>G	F508del/S1235R
rs199826652/ rs34911792	c.1521_1523delCTT/ c.3705T>G	F508del/S1235R
rs199826652/ rs755619078	c.1521_1523delCTT/ c.589T>C	F508del
rs199826652/ chr7:117509093:G:A	c.1521_1523delCTT/ c.224G>A	F508del/R75Q

rs199826652/ chr7:117509093:G:A	c.1521_1523delCTT/ c.224G>A	F508del/R75Q
rs199826652/ chr7:117509093:G:A	c.1521_1523delCTT/ c.224G>A	F508del/R75Q
rs199826652/ chr7:117509093:G:A	c.1521_1523delCTT/ c.224G>A	F508del/R75Q
rs199826652/ chr7:117509093:G:A	c.1521_1523delCTT/ c.224G>A	F508del/R75Q
rs199826652/ rs763914313	c.1521_1523delCTT/ c.727A>G	F508del
chr7:117611650:G:A/ chr7:117642528:G:A	c.3209G>A/ c.3808G>A	R1070Q / D1270N
chr7:117530975:G:A/ rs115545701 and chr7:117642528:G:A	c.350G>A/ c.2900T>C and c.3808G>A	R117H/ R74W and D1270N
rs121908759/ rs115545701 and chr7:117642528:G:A	c.1865G>A/ c.220C>T and c.3808G>A	G622D/ R74W and D1270N
rs115545701 and chr7:117642528:G:A/ rs115545701 and chr7:117642528:G:A	c.220C>T and c.3808G>A/ c.220C>T and c.3808G>A	R74W and D1270N/ R74W and D1270N
rs115545701 and chr7:117642528:G:A/ rs115545701 and chr7:117642528:G:A	c.220C>T and c.3808G>A/ c.220C>T and c.3808G>A	R74W and D1270N/ R74W and D1270N