

Online Depository - Supplementary material

Inclusion criteria and corticosteroid use in population 1 and 2

In population 1, main inclusion criteria were: FEV₁ ≥1.2 L, absence of bronchiectasis, upper respiratory tract infection (e.g. colds) and/or use of antibiotics or oral corticosteroids within the last 2 months before inclusion. Only 36.8% (21/57) of subjects on ICS treatment had stopped ICS medication for a minimum of four weeks before entering the study.

In population 2, before testing, participants had to be in stable condition without any exacerbation in the last 6 weeks and subjects were allowed to use maintenance medication before testing. Subjects included in the lung function decline analysis required having FEV₁ measurements before and after the introduction of ICS, with a minimum of three FEV₁ measurements over a period of at least 2 years. Subjects who never used ICS were excluded from the performed analysis.

Bronchial biopsies

After local anesthesia, at least 5 bronchial biopsies were obtained from the subsegmental carinas from the left or right lower lobe using a flexible bronchoscope (Olympus BF P20 or BF XT20). Biopsies were fixed in 4% formalin, processed and embedded in paraffin and cut in 3µm thick sections. Macroscopically the best biopsy was selected for processing. Quantification was performed on the largest of three biopsy sections. Morphological features were determined on sections stained with hematoxylin and eosin (HE) and with periodic acid Schiff. Immunohistochemical stainings (except for E-cadherin) were performed using the DAKO autostainer (DAKO, Glostrup, Denmark). The slides were included in a random fashion in each run to avoid group-wise staining. Immunohistochemistry was performed using antibodies

directed against CD8+T-cells (CD8, DAKO), CD31+endothelial cells (CD31, DAKO), eosinophilic peroxidase (EPX), epithelial adhesion (E-cadherin, BD Biosciences, Breda, the Netherlands). In short, sections were deparaffinized and after antigen retrieval, incubated with the primary antibodies. These antibodies were detected with Envision™ Detection Kit (DAKO) and the chromogen NovaRED (Vector Labs, Burlingame, USA). EPX was detected via biotinylated anti-mouse IgG1 (Southern Biotech), alkaline phosphatase-labeled conjugate (DAKO) and permanent Red (DAKO). E-cadherin were detected with two peroxidaselabelled conjugates (both DAKO) and 3,3'-Diaminobenzidine tetrahydrochloride (Sigma-Aldrich, Zwijndrecht, the Netherlands). All stainings were quantified by a blinded observer using computer-assisted image analysis at a magnification of 200x (Qwin, Leica Microsystems Imaging Solutions, Cambridge, UK). Inflammatory cell numbers were quantified by counting the number of positively stained cells in the submucosal area, 100µm under the basement membrane (BM), in a total area of 0.1mm² per biopsy sample. The number of CD31+ vessels in the submucosal area was counted in the whole section (excluding epithelium, muscle and mucus glands areas), hence we measured the number of vessels per area (0.1mm²). Epithelial layer integrity was assessed on HE-stained biopsy sections and expressed as the percentage of BM covered with 1) normal, intact epithelium (basal and ciliated columnar epithelial cells), 2) denuded epithelium (absence of basal and ciliated cells) and 3) metaplastic epithelium (multilayered epithelium covered by a flattened layer of squamous epithelial cells and absence of ciliated cells). The length of basement membrane was variable among patients with a minimum of 973µm. Epithelial adhesion was determined by assessment of the percentage of BM covered with E-cadherin+ intact epithelium. The (median [min-max]) length of basement membrane covered with intact epithelium analyzed in each biopsy was 605 [0-3147] µm. BM thickness was calculated based on computer-assisted measurements of BM surface area and BM length. Reproducibility of the

measurements was confirmed by a single observer performing repeated measurements in 10% of all cases.

Table E1: Genotype distributions in population 1 and 2

CDH1 gene SNPs	Location in gene	Alleles [^]	Population 1			Population 2		
			wt	htz	hmz	wt	htz	hmz
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
rs2902185 ^G	Intron 2	T:C	81 (78.6)	22 (21.4)	0 (0)	180 (78.6)	48 (21.0)	1 (0.4)
rs11075699	Intron 2	A:G	44 (32.1)	67 (48.9)	26 (19.0)	67 (27.0)	124 (50.0)	57 (23.0)
rs1125557	Intron 2	A:G	43 (32.1)	67 (50.0)	24 (17.9)	93 (39.1)	106 (44.5)	39 (16.4)
rs12597188	Intron 2	G:A	54 (39.7)	64 (47.1)	18 (13.2)	104 (41.9)	108 (43.5)	36 (14.5)
rs7199991 ^G	Intron 2	T:G	50 (48.5)	43 (41.7)	10 (9.7)	125 (54.6)	82 (35.8)	22 (9.6)
rs7186053	Intron 3	G:A	45 (32.8)	72 (52.6)	20 (14.6)	93 (37.2)	119 (47.6)	38 (15.2)
rs10431924	Intron 3	C:T	34 (24.8)	75 (54.7)	28 (20.4)	83 (33.9)	113 (46.1)	49 (20.0)
rs4783573	Intron 3	A:G	56 (41.2)	64 (47.1)	16 (11.8)	107 (43.5)	112 (45.5)	27 (11.0)
rs7188750 ^G	Intron 5	G:A	69 (67.0)	29 (28.2)	5 (4.9)	166(72.5)	56 (24.5)	7 (3.1)
rs8056633	Intron 9	T:G	72 (53.7)	56 (41.8)	6 (4.5)	137 (55.7)	90 (36.6)	19 (7.7)
rs4783689	Intron11	C:T	46 (33.8)	64 (47.1)	26 (19.1)	66 (26.6)	121 (48.8)	61 (24.6)
rs16958383	Intron12	G:A	94 (69.1)	38 (27.9)	4 (2.9)	183 (73.8)	58 (23.4)	7 (2.8)
rs2276330 ^G	Intron12	T:C	75 (72.8)	24 (23.3)	4 (3.9)	177 (77.3)	50 (21.8)	2 (0,9)
rs1801552 ^G	Exon13	C:T	46 (44.7)	48 (46.6)	9 (8.7)	116 (50.7)	91 (39.7)	22 (9.6)
rs3785078	Intron14	A:C	101 (75.4)	31 (23.1)	2 (1.5)	186 (75.0)	59 (23.8)	3 (1.2)
rs7203904	Intron14	G:C	70 (51.1)	58 (42.3)	9 (6.6)	133 (53.8)	91 (36.8)	23 (9.3)
rs17690554	3' UTR	C:G	86 (62.8)	47 (34.3)	4 (2.9)	145 (58.9)	89 (36.8)	12 (4.9)

[^]major allele first, ^G Genotyped in genome wide association study (GWAS) on asthma

SNPs= single nucleotide polymorphisms, wt: wild types, htz: heterozygotes and hmz: homozygotes mutant

Table E2: Associations of *CDH1* genotypes with epithelial E-cadherin expression in ICS and no ICS group

<i>CDH1</i> gene SNPs		% epithelial E-cadherin expression [#]					
		no ICS			ICS		
		N	MEDIAN	^{\$} P	N	MEDIAN	^{\$} P
rs2902185	TT	36	100	0.09	40	79	0.51
	TC/CC	15	66		7	59	
rs11075699	AA	17	79	0.31	23	72	0.15
	AG/GG	54	100		33	83	
rs1125557	AA	20	98	0.75	21	80	0.85
	AG/GG	49	100		34	89	
rs12597188	GG	30	98	0.61	22	81	0.88
	AG/AA	41	100		33	82	
rs7199991	AA	28	96	0.27	21	82	0.39
	AC/CC	23	100		26	71	
rs7186053	GG	25	87	0.15	18	79	0.99
	GA/AA	46	100		38	88	
rs10431924	CC	16	76	0.10	16	81	0.65
	CT/TT	55	100		40	83	
rs4783573	AA	30	100	0.84	20	75	0.33
	AG/GG	40	100		36	85	
rs7188750	GG	35	100	0.11	30	78	0.95
	GA/AA	16	79		17	80	
rs8056633	TT	41	100	0.04*	26	78	0.57
	TG/GG	28	83		29	82	
rs4783689	CC	31	91	0.20	11	78	0.50
	CT/TT	39	100		45	82	
rs16958383	GG	49	100	0.01*	38	82	0.99
	GA/AA	21	52		18	79	
rs2276330	TT	38	100	0.049*	33	78	0.43
	TC/CC	13	67		14	84	
rs1801552	CC	19	100	0.70	26	79	0.67
	CT/TT	32	100		21	79	
rs3785078	AA	55	100	0.03*	39	83	0.95
	AC/CC	14	54		16	79	
rs7203904	GG	39	100	0.04*	27	78	0.44
	GC/CC	32	82		29	83	
rs17690554	CC	48	100	0.11	32	79	0.36
	CG/GG	23	86		24	82	

*p value<0.05, ^{\$} significance tested with Mann–Whitney *U* test, [#] percentage of basement membrane covered with E-cadherin-positive stained intact epithelium, N= number of subjects

Table E3.1: Associations of *CDH1* genotypes with basement membrane thickness in ICS and no ICS group

<i>CDH1</i> gene SNPs		Basement membrane thickness (µm)								
		no ICS			ICS			Difference (ICS vs no ICS) [#]		
		B	95% CI	P	B	95% CI	P	B	95% CI	P
rs2902185	TC/CC	-0.63	(-1.59;0.32)	0.19	1.05	(-0.21;2.31)	0.10	1.68	(0.12;3.25)	0.036*
rs11075699	AG	0.05	(-0.72;0.83)	0.89	0.60	(-0.29;1.49)	0.18	0.55	(-0.62;1.72)	0.35
	GG	-0.12	(-1.17;0.92)	0.82	-0.02	(-1.07;1.04)	0.98	0.11	(-1.37;1.59)	0.89
rs1125557	AG	-0.67	(-1.48;0.13)	0.10	0.50	(-0.38;1.39)	0.27	1.17	(-0.03;2.37)	0.05
	GG	-0.23	(-1.31;0.86)	0.68	0.22	(-0.84;1.27)	0.69	0.44	(-1.07;1.95)	0.56
rs12597188	GA/AA	-0.06	(-0.74;0.63)	0.87	0.03	(-0.76;0.82)	0.94	0.06	(-0.96;1.20)	0.87
rs7199991	AC/CC	-0.14	(-1.01;0.73)	0.75	-0.25	(-1.17;0.67)	0.59	-0.11	(-1.39;1.16)	0.86
rs7186053	GA/AA	-0.45	(-1.17;0.27)	0.22	0.17	(-0.65;1.00)	0.68	0.62	(-0.48;1.72)	0.26
rs10431924	CT	-0.73	(-1.58;0.12)	0.09	0.04	(-0.87;0.95)	0.93	0.77	(-0.49;2.03)	0.23
	TT	-0.65	(-1.72;0.43)	0.24	0.22	(-0.85;1.28)	0.69	0.86	(-0.65;2.37)	0.26
rs4783573	AG/GG	0.31	(-0.37;1.00)	0.36	-0.04	(-0.86;0.78)	0.92	-0.35	(-1.43;0.73)	0.52
rs7188750	GA/AA	-0.15	(-1.08;0.77)	0.75	-0.86	(-1.79;0.08)	0.07	-0.71	(-2.03;0.61)	0.29
rs8056633	TG/GG	-0.56	(-1.22;0.11)	0.10	-0.67	(-1.43;0.09)	0.09	-0.11	(-1.13;0.90)	0.83
rs4783689	CT	0.03	(-0.73;0.79)	0.94	0.04	(-1.00;1.07)	0.94	0.01	(-1.27;1.29)	0.99
	TT	0.11	(-0.81;1.03)	0.81	0.33	(-0.98;1.65)	0.62	0.22	(-1.41;1.85)	0.79
rs16958383	GA/AA	-0.25	(-0.97;0.46)	0.48	-1.05	(-1.86;-0.24)	0.01*	-0.79	(-1.88;0.29)	0.15
rs2276330	TC/CC	0.09	(-0.90;1.08)	0.86	-1.08	(-2.07;-0.09)	0.03*	-1.17	(-2.60;0.26)	0.11
rs1801552	CT/TT	-0.55	(-1.44;0.34)	0.22	0.57	(-0.33;1.48)	0.21	1.12	(-0.14;2.38)	0.08
rs3785078	AC/CC	0.24	(-0.57;1.05)	0.56	-1.05	(-1.88;-0.22)	0.01*	-1.29	(-2.44;-0.13)	0.03*
rs7203904	GC/CC	-0.14	(-0.81;0.53)	0.68	-0.63	(-1.40;0.14)	0.11	-0.49	(-1.51;0.54)	0.35
rs17690554	CG/GG	-0.07	(-0.77;0.63)	0.84	-1.00	(-1.76;-0.24)	0.01*	-0.93	(-1.97;0.11)	0.08

*p value<0.05, [#]Difference= interaction of ICS with SNP

Table E3.2: Associations of *CDH1* genotypes with subepithelial vasculature in ICS and no ICS group

<i>CDH1</i> gene SNPs		Number of CD31+vessels per 0.1mm ² of submucosal area								
		no ICS			ICS			Difference (ICS vs no ICS) [#]		
		B	95% CI	P	B	95% CI	P	B	95% CI	P
rs2902185	TC/CC	0.66	(-4.51;5.82)	0.80	-1.01	(-7.88;5.85)	0.77	-1.67	(-10.18;6.84)	0.70
rs11075699	AG	1.20	(-2.94;5.34)	0.57	3.25	(-1.56;8.07)	0.18	2.05	(-4.25;8.35)	0.52
	GG	2.53	(-2.93;7.99)	0.36	3.05	(-2.62;8.71)	0.29	0.52	(-7.35;8.38)	0.90
rs1125557	AG	-1.70	(-5.95;2.55)	0.43	3.93	(-0.84;8.69)	0.11	5.63	(-0.79;12.04)	0.09
	GG	-0.84	(-6.64;4.96)	0.78	2.93	(-2.92;8.78)	0.32	3.77	(-4.43;11.97)	0.36
rs12597188	GA/AA	2.06	(-1.56;5.69)	0.26	4.08	(-0.16;8.32)	0.06	2.02	(-3.52;7.56)	0.47
rs7199991	AC/CC	0.02	(-4.57;4.62)	0.99	3.22	(-1.67;8.11)	0.19	3.20	(-3.54;9.93)	0.35
rs7186053	GA/AA	1.56	(-2.28;5.37)	0.42	2.02	(-2.42;6.46)	0.37	0.47	(-5.41;6.34)	0.88
rs10431924	CT	-0.91	(-5.41;3.59)	0.69	0.81	(-4.19;5.82)	0.75	1.72	(-5.05;8.50)	0.62
	TT	-0.28	(-6.04;5.48)	0.92	0.55	(-5.22;6.31)	0.85	0.83	(-7.27;8.92)	0.84
rs4783573	AG/GG	0.64	(-3.00;4.27)	0.73	1.73	(-2.71;6.16)	0.44	1.09	(-4.73;6.91)	0.71
rs7188750	GA/AA	-3.18	(-7.93;1.56)	0.19	-6.92	(-11.75;-2.09)	0.005*	-3.73	(-10.54;3.07)	0.28
rs8056633	TG/GG	-2.82	(-6.37;0.72)	0.12	-4.65	(-8.81;-0.49)	0.03*	-1.82	(-7.30;3.65)	0.51
rs4783689	CT	0.04	(-3.93;4.01)	0.98	3.86	(-1.77;9.49)	0.18	3.82	(-3.06;10.69)	0.27
	TT	2.37	(-2.48;7.22)	0.33	5.57	(-1.49;12.62)	0.12	3.19	(-5.49;11.88)	0.47
rs16958383	GA/AA	-3.41	(-7.19;0.37)	0.08	-6.11	(-10.40;-1.83)	0.005*	-2.70	(-8.43;3.03)	0.35
rs2276330	TC/CC	1.29	(-3.92;6.49)	0.63	-6.94	(-12.15;-1.73)	0.01*	-8.22	(-15.73;-0.71)	0.03*
rs1801552	CT/TT	-0.63	(-5.41;4.15)	0.79	0.65	(-4.28;5.59)	0.79	1.28	(-5.53;8.09)	0.71
rs3785078	AC/CC	-0.91	(-5.26;3.45)	0.68	-6.61	(-11.09;-2.13)	0.004*	-5.71	(-11.93;0.52)	0.07
rs7203904	GC/CC	-2.27	(-5.76;1.23)	0.20	-4.66	(-8.78;-0.54)	0.03*	-2.39	(-7.84;3.05)	0.39
rs17690554	CG/GG	-0.19	(-3.97;3.59)	0.92	-2.83	(-7.02;1.35)	0.18	-2.64	(-8.31;3.03)	0.36

*p value<0.05, [#]Difference= interaction of ICS with SNP

Table E4.1: Association of *CDH1* genotypes with CD8+T-cells in ICS and no ICS group

<i>CDH1</i> gene SNPs		Number of CD8+T-cells per 0.1mm ² of submucosal area (log-transformed)								
		no ICS			ICS			Difference (ICS vs no ICS) [#]		
		B	95% CI	P	B	95% CI	P	B	95% CI	P
rs2902185	TC/CC	-0.04	(-0.67;0.59)	0.90	-0.03	(-0.86;0.80)	0.94	0.01	(-1.02;1.04)	0.99
rs11075699	AG	-0.02	(-0.53;0.49)	0.93	0.62	(0.03;1.22)	0.04*	0.65	(-0.13;1.42)	0.10
	GG	-0.37	(-1.04;0.31)	0.28	-0.09	(-0.79;0.60)	0.79	0.28	(-0.69;1.25)	0.57
rs1125557	AG	0.47	(-0.04;0.99)	0.07	0.36	(-0.22;0.94)	0.22	-0.12	(-0.89;0.66)	0.77
	GG	0.30	(-0.40;1.00)	0.39	-0.73	(-1.42;-0.05)	0.04*	-1.04	(-2.02;-0.06)	0.04*
rs12597188	GA/AA	0.39	(-0.06;0.84)	0.09	-0.12	(-0.64;0.41)	0.66	-0.51	(-1.20;0.18)	0.14
rs7199991	AC/CC	0.38	(-0.17;0.94)	0.17	-0.29	(-0.88;0.29)	0.32	-0.68	(-1.48;0.13)	0.10
rs7186053	GA/AA	0.48	(0.00;0.95)	0.05	0.13	(-0.43;0.68)	0.65	-0.35	(-1.08;0.38)	0.35
rs10431924	CT	0.24	(-0.31;0.79)	0.40	0.53	(-0.08;1.14)	0.09	0.29	(-0.53;1.12)	0.49
	TT	0.32	(-0.39;1.02)	0.37	-0.26	(-0.96;0.45)	0.47	-0.57	(-1.56;0.42)	0.25
rs4783573	AG/GG	0.00	(-0.46;0.46)	0.99	0.02	(-0.54;0.57)	0.96	0.01	(-0.72;0.74)	0.97
rs7188750	GA/AA	-0.51	(-1.10;0.08)	0.09	0.53	(-0.07;1.12)	0.08	1.04	(0.20;1.87)	0.02*
rs8056633	TG/GG	-0.15	(-0.61;0.32)	0.53	0.05	(-0.49;0.59)	0.86	0.19	(-0.52;0.90)	0.59
rs4783689	CT	-0.08	(-0.57;0.42)	0.76	-0.65	(-1.34;0.03)	0.06	-0.58	(-1.42;0.27)	0.18
	TT	0.42	(-0.18;1.03)	0.17	-0.42	(-1.28;0.45)	0.34	-0.84	(-1.91;0.23)	0.12
rs16958383	GA/AA	-0.30	(-0.79;0.19)	0.23	0.30	(-0.26;0.87)	0.29	0.60	(-0.15;1.35)	0.11
rs2276330	TC/CC	-0.60	(-1.22;0.03)	0.06	0.80	(0.18;1.42)	0.01*	1.40	(0.51;2.30)	0.003*
rs1801552	CT/TT	-0.47	(-1.04;0.10)	0.11	0.05	(-0.53;0.64)	0.85	0.53	(-0.29;1.34)	0.20
rs3785078	AC/CC	-0.11	(-0.66;0.45)	0.70	0.36	(-0.22;0.94)	0.23	0.47	(-0.33;1.27)	0.25
rs7203904	GC/CC	-0.08	(-0.53;0.37)	0.73	0.24	(-0.29;0.77)	0.38	0.32	(-0.38;1.01)	0.37
rs17690554	CG/GG	0.01	(-0.46;0.48)	0.97	0.44	(-0.09;0.97)	0.10	0.43	(-0.28;1.14)	0.24

*p value<0.05, #Difference= interaction of ICS with SNPs

Table E4.2: Association of *CDH1* genotypes with eosinophilic peroxidase (EPX)+cells in ICS and no ICS group

<i>CDH1</i> gene SNPs		Number of EPX+cells per 0.1mm ² of submucosal area (log-transformed)								
		No ICS			ICS			Difference (ICS vs no ICS) [#]		
		B	95% CI	P	B	95% CI	P	B	95% CI	P
rs2902185	TC/CC	-0.01	(-0.65;0.63)	0.97	0.94	(0.11;1.77)	0.03*	0.95	(-0.09;1.99)	0.07
rs11075699	AG	0.06	(-0.50;0.61)	0.84	-0.16	(-0.79;0.47)	0.61	-0.22	(-1.05;0.61)	0.60
	GG	-0.06	(-0.78;0.67)	0.87	-0.49	(-1.23;0.26)	0.20	-0.43	(-1.47;0.61)	0.41
rs1125557	AG	-0.01	(-0.57;0.54)	0.96	0.40	(-0.22;1.03)	0.21	0.42	(-0.43;1.26)	0.33
	GG	-0.19	(-0.95;0.57)	0.63	0.56	(-0.18;1.31)	0.14	0.75	(-0.31;1.81)	0.16
rs12597188	GA/AA	0.12	(-0.37;0.62)	0.62	0.21	(-0.36;0.78)	0.46	0.09	(-0.66;0.83)	0.82
rs7199991	AC/CC	0.04	(-0.54;0.63)	0.88	0.07	(-0.54;0.67)	0.83	0.02	(-0.82;0.86)	0.96
rs7186053	GA/AA	0.05	(-0.46;0.55)	0.85	0.43	(-0.15;1.01)	0.14	0.38	(-0.39;1.15)	0.33
rs10431924	CT	-0.09	(-0.68;0.49)	0.75	0.03	(-0.61;0.67)	0.93	0.12	(-0.74;0.99)	0.78
	TT	-0.29	(-1.03;0.45)	0.44	0.81	(0.07;1.55)	0.03*	1.09	(0.05;2.14)	0.04*
rs4783573	AG/GG	0.10	(-0.38;0.58)	0.68	-0.33	(-0.91;0.24)	0.26	-0.43	(-1.19;0.33)	0.26
rs7188750	GA/AA	-0.24	(-0.86;0.38)	0.45	0.21	(-0.42;0.83)	0.51	0.44	(-0.44;1.33)	0.32
rs8056633	TG/GG	-0.17	(-0.65;0.31)	0.49	-0.04	(-0.59;0.51)	0.89	0.13	(-0.61;0.86)	0.73
rs4783689	CT	-0.02	(-0.55;0.51)	0.94	0.46	(-0.27;1.18)	0.21	0.48	(-0.42;1.37)	0.29
	TT	0.14	(-0.50;0.78)	0.66	0.74	(-0.17;1.66)	0.11	0.60	(-0.54;1.74)	0.30
rs16958383	GA/AA	-0.38	(-0.90;0.14)	0.15	0.16	(-0.42;0.75)	0.58	0.55	(-0.24;1.33)	0.17
rs2276330	TC/CC	-0.20	(-0.87;0.48)	0.57	0.29	(-0.38;0.95)	0.39	0.48	(-0.48;1.45)	0.32
rs1801552	CT/TT	-0.33	(-0.92;0.27)	0.28	-0.16	(-0.77;0.44)	0.60	0.16	(-0.68;1.00)	0.70
rs3785078	AC/CC	0.13	(-0.46;0.73)	0.66	-0.01	(-0.62;0.59)	0.96	-0.15	(-1.00;0.70)	0.73
rs7203904	GC/CC	-0.17	(-0.65;0.31)	0.48	-0.06	(-0.61;0.49)	0.84	0.11	(-0.62;0.84)	0.76
rs17690554	CG/GG	0.15	(-0.35;0.65)	0.56	-0.01	(-0.56;0.54)	0.97	-0.16	(-0.91;0.59)	0.68

*p value<0.05, [#]Difference= interaction of ICS with SNPs

Table E5: Effect of *CDH1* genotypes on annual change in lung function before and after the introduction of ICS

<i>CDH1</i> gene SNPs		FEV ₁ annual change in population 2 (ml/year)								
		no ICS			ICS			Difference (ICS vs no ICS) [#]		
		Annual change in WT	Difference in annual change compared to WT		Annual change in WT	Difference in annual change compared to WT		Annual change in WT	Difference in annual change compared to WT	
	B (95%CI)	P		B (95%CI)	P		B (95%CI)	P		
rs2902185	TT TC/CC	-21.6	-17.5 (-38.8;3.8)	0.11	-17.4	-3.7 (-16.40;8.96)	0.57	4.1	13.7 (-10.4;37.9)	0.26
rs11075699	AA AG GG	-25.9	-1.3 (-20.6;18.1) 1.8 (-20.8;24.5)	0.90 0.87	-20.3	1.0 (-11.77;13.74) 7.67 (-8.33;23.68)	0.35 0.38	5.5	2.2 (-20.1;24.6) 5.9 (-21.1;32.8)	0.84 0.67
rs1125557	AA AG GG	-22.7	-5.4 (-21.8;11.1) -1.1 (-24.2;22.0)	0.52 0.93	-7.6	-19.7 (-32.0;-7.4) -17.6 (-33.0;-2.3)	0.002* 0.024*	-7.6	-14.3 (-34.5;5.9) -16.6 (-43.7;10.6)	0.16 0.23
rs12597188	GG GA AA	-23.2	-6.5 (-22.8;9.7) -3.2 (-25.0;18.5)	0.43 0.77	-17.1	-1.6 (-13.8;10.7) -2.2 (-18.0;13.7)	0.80 0.79	6.2	5.0 (-14.7;24.6) 1.1 (-25.0;27.1)	0.62 0.94
rs7199991	AA AC CC	-29.9	7.8 (-9.8;25.4) 16.5 (-7.0;40.0)	0.39 0.17	-15.0	-13.5 (-25.0;-1.9) -5.1 (-20.6;10.4)	0.023* 0.52	14.9	-21.3 (-41.3;-1.2) -21.7 (-48.8;5.4)	0.04* 0.12
rs7186053	GG GA AA	-25.8	-1.7 (-18.4;15.0) -6.1 (-29.5;17.3)	0.84 0.61	-8.7	-16.7 (-28.2;-5.1) -13.7 (-28.8;1.5)	0.005* 0.08	17.1	-15.0 (-34.6;4.6) -7.6 (-34.5;19.3)	0.13 0.58
rs10431924	CC CT TT	-25.8	-2.7 (-20.5;15.1) -6.0 (-27.6;15.6)	0.76 0.58	-14.0	-4.6 (-18.1;8.9) -12.1 (-26.7;2.5)	0.51 0.10	11.8	-1.9 (-23.3;19.5) -6.1 (-31.0;18.7)	0.86 0.63
rs4783573	AA AG GG	-24.9	-2.9 (-18.9;13.1) 10.1 (-15.2;35.5)	0.43 0.98	-20.7	4.7 (-6.8;16.2) 19.2 (-1.5;39.8)	0.43 0.07	4.3	7.6 (-11.4;26.5) 9.0 (-22.6;40.6)	0.43 0.58

rs7188750	GG GA/AA	-25.8	0.4 (-20.7;21.6)	0.97	-19.2	5.6 (-6.6;17.7)	0.37	6.6	5.2 (-18.2;28.5)	0.66
rs8056633	TT TG GG	-28.3	6.5 (-10.6;23.6) 6.2 (-18.5;30.8)	0.46 0.62	-23.0	8.6 (-3.9;21.1) 27.2 (14.2;40.3)	0.18 <0.001	5.3	2.2 (-18.1;22.3) 21.1 (-5.6;47.7)	0.84 0.12
rs4783689	CC CT TT	-21.6	-4.8 (-23.6;14.0) -8.3 (-29.2;12.5)	0.62 0.43	-13.6	-6.4 (-20.9;8.1) -4.1 (-20.5;12.3)	0.39 0.62	7.9	-1.6 (-24.8;21.5) 4.2 (-21.8;30.2)	0.89 0.75
rs16958383	GG GA AA	-25.3	-10.8 (-30.2;8.6) 4.4 (-28.1;36.9)	0.27 0.79	-20.4	10.5 (-2.1;23.2) 36.6(11.9;61.3)	0.10 0.004*	4.9	21.4 (-0.8;43.5) 32.2 (-6.4;70.8)	0.06 0.10
rs2276330	TT TC/CC	-25.4	-11.1 (-34.9;12.8)	0.36	-19.1	6.7 (-6.3;19.6)	0.31	6.2	17.7 (-8.1;43.6)	0.18
rs1801552	CC CT TT	-27.5	5.9 (-12.9;24.7) 1.2 (-26.9;29.2)	0.54 0.94	-15.0	-7.5 (-25.8;10.9) -7.2 (-18.5;4.1)	0.44 0.21	12.5	-13.4 (-34.9;8.1) -86 (-40.6;23.9)	0.22 0.61
rs3785078	AA AC/CC	-24.4	-10.6 (-28.6;7.4)	0.25	-20.0	10.5 (-1.9;22.9)	0.10	4.3	21.1 (0.4;41.8)	0.05
rs7203904	GG GC CC	-24.6	-3.9 (-20.8;13.1) 6.0 (-21.4;33.5)	0.66 0.67	-22.3	1.7 (-9.7;13.0) 27.4 (13.4;41.4)	0.78 <0.001	2.3	5.5 (-14.1;25.2) 21.4 (-8.6;51.3)	0.58 0.16
rs17690554	CC CG GG	-25.3	-2.2 (-18.8;14.5) 20.2 (-37.2;77.61)	0.80 0.49	-23.5	15.3 (4.0;26.6) 26.9 (7.2;46.5)	0.008* 0.007*	1.8	17.4 (-1.5;36.2) 6.7 (-51.4;64.7)	0.07 0.82

*p value<0.05, #Difference=interaction of ICS with SNP, FEV₁=forced expiratory volume in one second, WT=wild types

Table E6.1: Associations of *CDH1* genotypes with FEV₁/VC post bronchodilator in ICS and no ICS group in population 1

<i>CDH1</i> gene SNPs		FEV ₁ /VC post bronchodilator population 1 (%)								
		no ICS			ICS			Difference (ICS vs no ICS) [#]		
		B	95% CI	P	B	95% CI	P	B	95% CI	P
rs2902185	TC/CC	-0.59	(-6.30;5.11)	0.84	-6.25	(-13.47;0.98)	0.09	-5.65	(-14.73;3.42)	0.22
rs11075699	AG	-1.37	(-5.91;3.17)	0.55	3.67	(-1.48;8.82)	0.16	5.03	(-1.76;11.83)	0.15
	GG	-3.05	(-8.97;2.87)	0.31	2.32	(-3.76;8.40)	0.45	5.37	(-3.11;13.85)	0.21
rs1125557	AG	2.51	(-2.08;7.11)	0.28	1.01	(-4.09;6.11)	0.70	-1.50	(-8.41;5.40)	0.67
	GG	4.36	(-1.86;10.57)	0.17	-1.74	(-7.83;4.36)	0.57	-6.09	(-14.76;2.58)	0.17
rs12597188	GA/AA	3.11	(-0.91;7.13)	0.13	0.39	(-4.22;4.99)	0.87	-2.72	(-8.79;3.34)	0.38
rs7199991	AC/CC	1.80	(-3.30;6.90)	0.49	0.53	(-4.69;5.75)	0.84	-1.27	(-8.56;6.02)	0.73
rs7186053	GA/AA	2.86	(-1.36;7.07)	0.18	1.01	(-3.76;5.77)	0.68	-1.85	(-8.22;4.53)	0.57
rs10431924	CT	3.94	(-0.87;8.76)	0.11	4.68	(-0.51;9.86)	0.08	0.73	(-6.37;7.83)	0.84
	TT	2.61	(-3.49;8.72)	0.40	-1.57	(-7.61;4.47)	0.61	-4.19	(-12.72;4.35)	0.33
rs4783573	AG/GG	-1.37	(-5.32;2.59)	0.50	0.30	(-4.43;5.02)	0.90	1.66	(-4.58;7.91)	0.60
rs7188750	GA/AA	-2.52	(-7.90;2.85)	0.35	2.61	(-2.73;7.96)	0.33	5.14	(-2.47;12.74)	0.18
rs8056633	TG	-0.62	(-4.63;3.40)	0.76	-1.81	(-6.42;2.80)	0.44	-1.19	(-7.31;4.93)	0.70
	GG	1.21	(-9.11;11.53)	0.82	9.29	(-0.94;19.53)	0.07	8.08	(-6.57;22.73)	0.28
rs4783689	CT	2.73	(-1.61;7.07)	0.22	-4.40	(-10.29;1.49)	0.14	-7.13	(-14.44;0.18)	0.06
	TT	0.40	(-4.87;5.66)	0.88	-5.99	(-13.45;1.47)	0.11	-6.39	(-15.67;2.90)	0.18
rs16958383	GA/AA	0.41	(-3.88;4.70)	0.85	0.53	(-4.27;5.33)	0.83	0.12	(-6.34;6.58)	0.97
rs2276330	TC/CC	-3.86	(-9.61;1.88)	0.18	3.63	(-2.03;9.29)	0.21	7.49	(-0.72;15.70)	0.07
rs1801552	CT/TT	-0.26	(-5.48;4.96)	0.92	1.42	(-3.80;6.65)	0.59	1.68	(-5.63;9.00)	0.65
rs3785078	AC/CC	-0.80	(-5.71;4.11)	0.75	1.92	(-3.07;6.92)	0.45	2.72	(-4.24;9.69)	0.44
rs7203904	GC	0.28	(-3.68;4.23)	0.89	-2.16	(-6.79;2.47)	0.36	-2.44	(-8.54;3.67)	0.43
	CC	-1.18	(-10.24;7.88)	0.80	8.95	(0.82;17.08)	0.03*	10.13	(-2.19;22.45)	0.11
rs17690554	CG/GG	-1.87	(-6.03;2.30)	0.38	2.17	(-2.34;6.67)	0.34	4.03	(-2.11;10.17)	0.20

*p value<0.05, [#]Difference= interaction of ICS with SNP, FEV₁= forced expiratory volume in one second, VC= vital capacity

Table E6.2: Associations of *CDH1* genotypes with FEV₁/VC post bronchodilator in ICS and no ICS group in population 2

<i>CDH1</i> gene SNPs		FEV ₁ /VC post bronchodilator population 2 (%)								
		no ICS			ICS			Difference (ICS vs no ICS) [#]		
		B	95% CI	P	B	95% CI	P	B	95% CI	P
rs2902185	TC/CC	-0.08	(-4.63;4.48)	0.97	-4.63	(-9.52;0.27)	0.06	-4.55	(-11.24;2.15)	0.18
rs11075699	AG	-0.69	(-5.51;4.12)	0.78	2.55	(-1.85;6.96)	0.26	3.25	(-3.25;9.74)	0.33
	GG	-3.45	(-9.25;2.34)	0.24	-0.18	(-5.42;5.05)	0.95	3.27	(-4.54;11.09)	0.41
rs1125557	AG	1.16	(-3.21;5.52)	0.60	1.69	(-2.59;5.96)	0.44	0.53	(-5.51;6.57)	0.86
	GG	3.79	(-2.54;10.12)	0.24	-4.18	(-9.57;1.20)	0.13	-7.97	(-16.28;0.33)	0.06
rs12597188	GA	2.18	(-1.96;6.32)	0.30	1.17	(-3.02;5.37)	0.58	-1.01	(-6.88;4.85)	0.73
	AA	0.21	(-6.67;7.09)	0.95	-0.75	(-6.03;4.54)	0.78	-0.96	(-9.68;7.77)	0.83
rs7199991	AC/CC	1.10	(-2.82;5.01)	0.58	0.89	(-3.07;4.84)	0.66	-0.21	(-5.74;5.31)	0.94
rs7186053	GA	1.78	(-2.32;5.89)	0.39	-2.16	(-6.25;1.93)	0.30	-3.94	(-9.71;1.83)	0.18
	AA	-0.86	(-6.90;5.18)	0.78	-4.59	(-9.98;0.80)	0.09	-3.73	(-11.77;4.31)	0.36
rs10431924	CT	1.39	(-2.92;5.70)	0.53	-1.45	(-5.89;2.99)	0.52	-2.84	(-8.99;3.31)	0.36
	TT	0.20	(-5.62;6.01)	0.95	-1.82	(-6.99;3.35)	0.49	-2.02	(-9.73;5.70)	0.61
rs4783573	AG	-3.22	(-7.35;0.91)	0.13	3.58	(-0.39;7.55)	0.08	6.80	(1.09;12.51)	0.02*
	GG	-2.76	(-8.67;3.15)	0.36	8.36	(1.38;15.35)	0.02*	11.12	(1.98;20.27)	0.02*
rs7188750	GA/AA	-1.84	(-6.00;2.31)	0.38	5.19	(0.70;9.69)	0.02*	7.03	(0.95;13.12)	0.02*
rs8056633	TG/GG	-2.89	(-6.67;0.88)	0.13	7.14	(3.33;10.94)	<0.001*	10.03	(4.64;15.41)	<0.001*
rs4783689	CT	-0.39	(-4.97;4.20)	0.87	-3.54	(-8.17;1.08)	0.13	-3.16	(-9.69;3.37)	0.34
	TT	-0.22	(-5.58;5.15)	0.94	-4.67	(-9.95;0.61)	0.08	-4.45	(-11.96;3.05)	0.24
rs16958383	GA/AA	-0.81	(-5.04;3.41)	0.70	5.50	(1.09;9.91)	0.01*	6.31	(0.23;12.39)	0.042*
rs2276330	TC/CC	-0.84	(-5.24;3.56)	0.71	4.48	(-0.43;9.39)	0.07	5.32	(-1.23;11.87)	0.11
rs1801552	CT/TT	2.21	(-1.62;6.05)	0.26	0.88	(-3.03;4.79)	0.66	-1.34	(-6.83;4.16)	0.63
rs3785078	AC/CC	-1.64	(-5.96;2.67)	0.45	6.07	(1.68;10.45)	0.01*	-1.34	(-6.83;4.16)	0.63
rs7203904	GC	-2.45	(-6.48;1.57)	0.23	5.14	(1.12;9.17)	0.01*	7.60	(1.88;13.31)	0.01*
	CC	-3.24	(-9.76;3.28)	0.33	9.84	(3.08;16.59)	<0.001*	13.08	(3.71;22.45)	0.01*
rs17690554	CG/GG	-2.63	(-6.37;1.11)	0.17	7.45	(3.66;11.24)	<0.001*	10.08	(4.77;15.40)	<0.001*

*p value<0.05, #Difference= interaction of ICS with SNP, FEV₁= forced expiratory volume in one second, VC= vital capacity