Heritability and genome wide association study of diffusing capacity of the lung (DLCo)

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Rotterdam study

The Rotterdam Study is an ongoing prospective population-based cohort study aimed at investigating the occurrence and risk factors of chronic diseases in the general population. The objectives and methods of the Rotterdam Study have been published previously (9). Briefly, the Rotterdam Study includes 3 cohorts encompassing 14,926 participants aged ≥ 45 years, living in Ommoord, a well-defined suburb of the city of Rotterdam, the Netherlands. Baseline data were collected between 1990 and 1993 (n = 7,983), between 2000 and 2003 (n = 3,011), and between 2006 and 2008 (n = 3,932); thereafter, examinations have been conducted every 4 to 5 years in all cohorts. DLCO was measured between 2009-2013.

Framingham Heart Study

In 1948, residents of Framingham, Massachusetts, were recruited for the first round of the Framingham Heart Study (FHS). The FHS Original Cohort included a total of 5,209 participants aged between 28 and 62 years. In 1971, the FHS Offspring Cohort was established, including 5,124 participants who were either the children of the Original Cohort or spouses. Finally, in 2002, the FHS Third Generation Cohorts was established, existing of 4,095 adults who were the children of the Offspring Cohort. DLCO was measured at the at the 8th and 9th examinations of the Offspring Cohort (2005-2008 and 2011-2014) and the 1st and 2nd examinations of the Third Generation Cohort (2002-2005 and 2008-2011). In addition to nuclear families, more distantly related individuals (e.g. cousins) were also included in the analyses. For participants with measurements at both time points, we used the later measurement in the analysis.

Lung function

DLCO (mmol/min/kPA) measured using the single breath technique in accordance with ERS / ATS guidelines (1). The alveolar volume (VA) was measured simultaneously by the single-breath helium technique. The DLCO per alveolar volume (DLCO/VA (mmol/min/kPA/liter)) was calculated as the DLCO divided by the VA. In the Rotterdam Study, these measurements were made using Master Screen® PFT Pro (CareFusion, San Diego, CA). In the Framingham Heart Study, these measurements were made using the Collins CPL System (nSpire Health, Inc., Longmont, CO). For this study, analyses were restricted to participants with two interpretable and reproducible measurement. Two measurements were considered as reproducible if the difference between the first and the second DLCO (mmol/min/kPA) measurement was equal or less than 10% and if the difference between the first and the second DLCO/VA (mmol/min/kPA/L) measurement was equal or less than 15%. In addition, the inspiratory volume “VIN” measured in liter during the diffusion test must be greater than or equal to 85% of the personal best value of the inhaled vital capacity “VC IN” measured in liters during the spirometry test. In case VC is lacking, predicted volumes were used. Finally outliers, defined as the mean ± 4 standard deviations, were excluded from all analyses.

Genetics

Rotterdam study participants were genotyped using the Illumina 550L, 550K duo or 610 quad arrays. Framingham participants were genotyped using the Affymetrix 500K array supplemented by the Affymetrix MIPS 50K. Samples with: call rate below 97.5% in Rotterdam and 97.0% in Framingham, gender mismatch, excess autosomal heterozygosity, duplicates or family relations (the Rotterdam Study only) and ethnic outliers were excluded. We also excluded variants with minor allele frequency <1%, call rate <95% (the Rotterdam Study) or 97% (the Framingham Heart Study), failing missingness tests, Hardy-Weinberg equilibrium (p-value < 10^{-6}). Genotypes were imputed using MACH/minimac software to the 1000 Genomes reference panel (phase I version 3).

Heritability

Heritability was defined as the ratio of trait variance due to additive genetic effects to the total phenotypic variance after accounting for covariates. To estimated heritability in unrelated individuals restricted maximum likelihood (REML) estimates were produced using the Genome-wide Complex Trait Analysis (GCTA) software (2). For this analysis, we filtered on allele frequency (MAF < 1%) and imputation quality (R^2 < 0.5). Additional pair-wise calculations were performed to estimate genetic relatedness between all individuals. For each pair with genetic similarity of > 0.025, one person was excluded. To estimate heritability based on known familial relationships, the Sequential Oligogenic Linkage Analysis Routines (SOLAR) software (3) was used to compute the maximum likelihood estimates of heritability. In both heritability analyses (GCTA and SOLAR) an inverse normal rank transformation was performed on the DLCO and DLCO/VA measures to ensure a normal distribution of the phenotypes. Heritability analyses were adjusted for age, sex and principal components of genetic relatedness ((PC) in GCTA only). Additional adjustment for current and former smoking were done in a subsequent analysis.

Genetic correlations

Genetic correlation analyses were performed using the LD score regression (4). We investigated the genetic correlation between DLCO and DLCO/VA (age-, sex- and smoking, weight, height and PC-adjusted models). The phenotypic correlation between DLCO and DLCO/VA was also investigated using the Pearson correlation. In addition, we investigated the genetic correlation between DLCO and DLCO/VA and previously published GWAS of FEV_1/FVC (5) and height (6). For the correlation with height age, sex and PC-adjusted model was used to estimate genetic overlap, and the fully adjusted model was used to investigate residual confounding by height. P-value of 0.05 was used as threshold of significance.

Overlap with reported COPD and emphysema GWAS associations

We examined the association with DLCO and DLCO/VA of 79 genetic loci for which replicated genome wide significant associations with COPD have been reported (7). A P-value of 0.05/79= 6.3 x 10-4 was used as the threshold of significance in this analysis. We also investigated the association with DLCO and DLCO/VA of 7 genetic loci of which genome-wide significant association with emphysema have been previously reported (8). A p-value of 0.05/7= 0.007 was used as the threshold of significance.

FINEMAP

We used FINEMAP (9) in order to calculate the posterior probability of the association on chromosome 6 being causal. Other than doing conditional association analysis to detect multiple signals at one locus, followed by an estimation of posterior probability of causality for each independent signal, this method uses the multiple causal variant assumption to calculate those probabilities efficiently and more accurately (10). For this analysis, we created the LD matrix from the Rotterdam Study cohort RS3 with n= 3,048 individuals and we extracted a 6 mega base region centred on rs17280293 with 8,371 SNPs (MAF>1%).

ADGRG6 mRNA expression in lung tissue of patients with or without COPD

Human study populations

Lung resection specimens were obtained from 92 patients, of which 78 from surgery for solitary pulmonary tumours (Ghent University Hospital, Ghent, Belgium) and 14 from explant lungs of end-stage COPD patients undergoing lung transplantation (University Hospital Gasthuisberg, Leuven, Belgium). Lung tissue at maximum distance from the pulmonary lesions and without signs of retro-obstructive pneumonia or tumour invasion was collected by a pathologist. None of the patients operated for malignancy were treated with neo-adjuvant chemotherapy. Written informed consent was obtained from all subjects. This study was approved by the medical ethical committees of the Ghent University Hospital (2011/14) and the University Hospital Gasthuisberg Leuven (S51577).

Definitions

Smoking was categorized in never, former and current. Former-smokers were defined as being abstinent of smoking for at least one year. COPD diagnosis and severity was defined using pre-operative spirometry according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification 1. Median values were used to define DLCO categories.

RNA extraction and real-time PCR-analysis

RNA was extracted with the miRNeasy Mini kit (Qiagen) from total lung tissue blocks submersed in RNA-later. cDNA was obtained by the miScript II RT kit (Qiagen), following manufacturer’s instructions. Expression of target genes ADGRG6 (GPR126) and reference genes Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), Hypoxanthine phosphoribosyltransferase-1 (HPRT-1) and Succinate Dehydrogenase Complex Flavoprotein Subunit A (SDHA) were analyzed using

Taqman Gene Expression Assays (Applied Biosystems, Forster City, CA, USA). Real-time PCR reactions were set up in duplicate using diluted cDNA using identical amplification conditions for each of the target and reference genes. A standard curve derived from serial dilutions of a mixture of all samples were included in each run. The amplification conditions consisted of: 10 minutes at 95°C and 60 cycles of 95°C for 10 seconds and 60°C for 15 seconds. Amplifications were performed using a LightCycler 96 detection system (Roche). Data were processed using the standard curve method. Expression of target genes was corrected by a normalization factor that was calculated based on the expression of three reference genes, using the geNorm applet according to the guidelines and theoretical framework previously described (11).

Statistical analysis

Statistical analysis was performed with Sigma Stat software (SPSS 19.0, Chicago, IL, USA), using Kruskal-Wallis, Mann-Whitney U, Fisher's exact test and Spearman correlation analysis. Characteristics of the study population are expressed as median and interquartile range. Linear regression was used to test the association between mRNA expression as determinant and DLCO/VA. Analyses were adjusted for age and sex in model 1 and additionally for smoking, weight and height in model 2. P-value of lower than 0.05 was considered statistically significant.

Supplemental results

Haemoglobin-adjusted analysis

Measures of DLCO and DLCO/VA are affected by haemoglobin (Hb) levels, since low levels of Hb can underestimate the true diffusing capacity potential of the lung (12). Only in the Rotterdam Study, DLCO and DLCO/VA measures which were corrected for Hb levels, were available. As a sensitivity analysis, we performed GWAS with Hb-corrected data in Rotterdam study (n=2,573). This confirmed the results of the analyses without Hb-correction.

FEV_1/FVC adjusted analysis

A significant association between the observed association at 6q24.1 (rs17280293, gene: *ADGRG6*; MAF: 0.22, P-value= 1.4 x 10^{-10}) and FEV_1/FVC was recently identified; (13) therefore, as a sensitivity analysis, we performed the DLCO/VA GWAS, with additional adjustment for FEV_1/FVC. This analysis, did not materially affect the association between rs17280293 and DLCO/VA (beta=-0.07 (SE: 0.01), P-value= 1.51 x 10^{-10}) *versus* (beta=-0.07 (SE 0.01), P-value= 7.9 x 10^{-11} without adjustment for FEV_1/FVC in model 2). **Figure E2** presents a double Manhattan plot with DLCO/VA before and after additional adjustment for FEV_1/FVC.

Follow-up analyses

Genetic correlations

We examined the genetic correlation between DLCO/VA and DLCO using the age, sex, smoking status, weight, height and PC adjusted model. The genetic correlation was 59% (ρgenetic=0.59, P-value=0.04). We also examined the genetic correlation between DLCO and DLCO/VA and FEV_1/FVC using the same model. Here we found no statistically significant genetic overlap between the traits. Finally, we examined the genetic correlation between the age-, sex- and PC-adjusted DLCO and

DLCO/VA and height. We found a significant genetic correlation between DLCO and height (ρgenetic=0.63, P-value=8.0e-4), and between DLCO/VA and height (ρgenetic=-0.16, P-value=0.01). We did not find a genetic correlation between DLCO and DLCO/VA and height in the age,sex, smoking status, weight, height and PC adjusted model.

Overlap with reported COPD and emphysema GWAS associations

We investigated the overlap between replicated genome-wide significant variants associated with COPD (7) (n=74) and variants associated with DLCO and DLCO/VA GWAS in both of our models (**Tables E4-E7** in the Online Data Supplement). Seven COPD-associated variants; rs9403391, rs13192074, rs11853359, rs9399401, rs2039987, rs1441358 and rs2415116 in the following gene regions RS11-440G9.1, ADGRG6 and THSD4 were significantly associated with DLCO/VA (**Tables E6 and E7** in the Online Data Supplement). No overlap was found between COPD-associated variants and those associated with DLCO.

We also investigated the association with DLCO and DLCO/VA of 7 genetic loci of which genome-wide significant association with emphysema have been previously reported (8), (since 7 out of 10 emphysema-associated variants were available in our results). No genetic overlap was found between the seven emphysema-associated variants and those associated with DLCO. Only one emphysema-related variant on chromosome 15 (rs55676755, gene: CHRNA3) was found to be also significantly associated with DLCO/VA (**Table E8** in the Online Data Supplement). Since variants in the CHRNA3 gene have been implicated in nicotine addiction, our study adds decreased DLCO/VA to the phenotypes associated with CHRNA3 genetic variation.

FINEMAP

To identify whether the observed signal in chromosome 6 on DLCO/VA is driven by the lead variant or by other variants in the same locus, we calculated the posterior probability of causality for variants in that region using the FINEMAP software (9). The lead variant rs17280293 had a posterior probability of causality of 0.72, the highest probability among all SNPs in the same region on chromosome 6. Rs148274477 was ranked second; however, the probability of causality for this variant was only 0.18, indicating that the signal in this region on chromosome 6 is mainly driven by rs17280293.

Functional annotation

Functional annotation of the variants of **Table 3** was performed in Haploreg. Haploreg analyses revealed several associations between regulatory chromatin marks, promotor histone marks, and enhancer histone marks with the SNPs in different tissue cell lines including foetal lung fibroblast cell lines and lung carcinoma cell lines (see **Figure E3** in the Online Data Supplement).

We also investigated in GTEx lung tissue database whether rs17280293 and the missense variant rs11155242 (D'=1 with rs17280293) were associated with mRNA expression of *ADGRG6* (eQTL). Unfortunately, the minor allele count (MAC) of rs17280293 was very low (MAC=11) and therefore the results of the eQTL analysis for this SNP were considered unreliable. On the other hand, we found a significant association between rs11155242 and mRNA expression of *ADGRG6* (Variant ID: 6_142691549_A_C_b37, β= -0.10, SE=0.05, p-value=0.03, MAC=124). (See **Figure E**5 in Online Data Supplement)

***ADGRG6* expression**

We checked the functionality of the *ADGRG6* gene in the Genotype-tissue expression (GTEx) portal, to identify tissue specific expression. *ADGRG6* showed to be highly expressed in the lung (n=427), with median expression of 19.26 reads per kilobase of transcript per million mapped reads (**Figure E4** in the Online Data Supplement). We additionally extracted mRNA from lung resection specimens of 92 patients who underwent surgery for solitary pulmonary tumours or lung transplantation, including 44 patients without COPD and 48 patients with COPD (**Table 4 in the main manuscript**). The mRNA expression of *ADGRG6* was significantly lower in lung tissue of patients with decreased DLCO/VA compared with patients with normal DLCO/VA (**Figure 5A in the main manuscript**) and in subjects with COPD (encompassing different categories of COPD severity according to the GOLD spirometric classification) compared to never smoking controls (**Figure 5B in the main manuscript)**. The *ADGRG6* mRNA levels were significantly associated with DLCO/VA after adjustment for age and sex in model 1 (n=67 β=0.85 (95% CI 0.06-1.64)) and after additional adjustment for weight, height and smoking in model 2 n=66 (β=0.75(95% CI 0.03-1.47)).

Supplementary tables and figures

Figure E1 Quantile-quantile plot at meta-analysis level

Table E1 Main results of the meta-analysis in the Rotterdam Study (RS)

Table E2. Main results of the GWAS in the Framingham Heart Study (FHS)

Table E3 Results of the meta-analysis in both cohorts; the Rotterdam Study and the Framingham Heart Study

Figure E2 Double Manhattan-plot where results of the meta-analysis of DLCO/VA before and after adjustment with FEV_1/FVC in model 2

Table E4 Overlap with reported COPD-associated variants and those associated with DLCO in Model 1

Table E5 Overlap with reported COPD-associated variants and those associated with DLCO in Model 2

Table E6 Overlap with reported COPD-associated variants and those associated with DLCO/VA in Model 1

Table E7 Overlap with reported COPD-associated variants and those associated with DLCO/VA in Model 2

Table E8 Overlap with reported emphysema-associated variants and those associated with DLCO and DLCO/VA in the models 1 and 2

Figure E3 Haploreg analysis of the main results of the meta-analysis

Figure E4 GTEx output of *ADGRG6* expression in different tissues

Figure E5 The genotypes of rs17280293 and rs11155242 in GTEx lung tissue database.

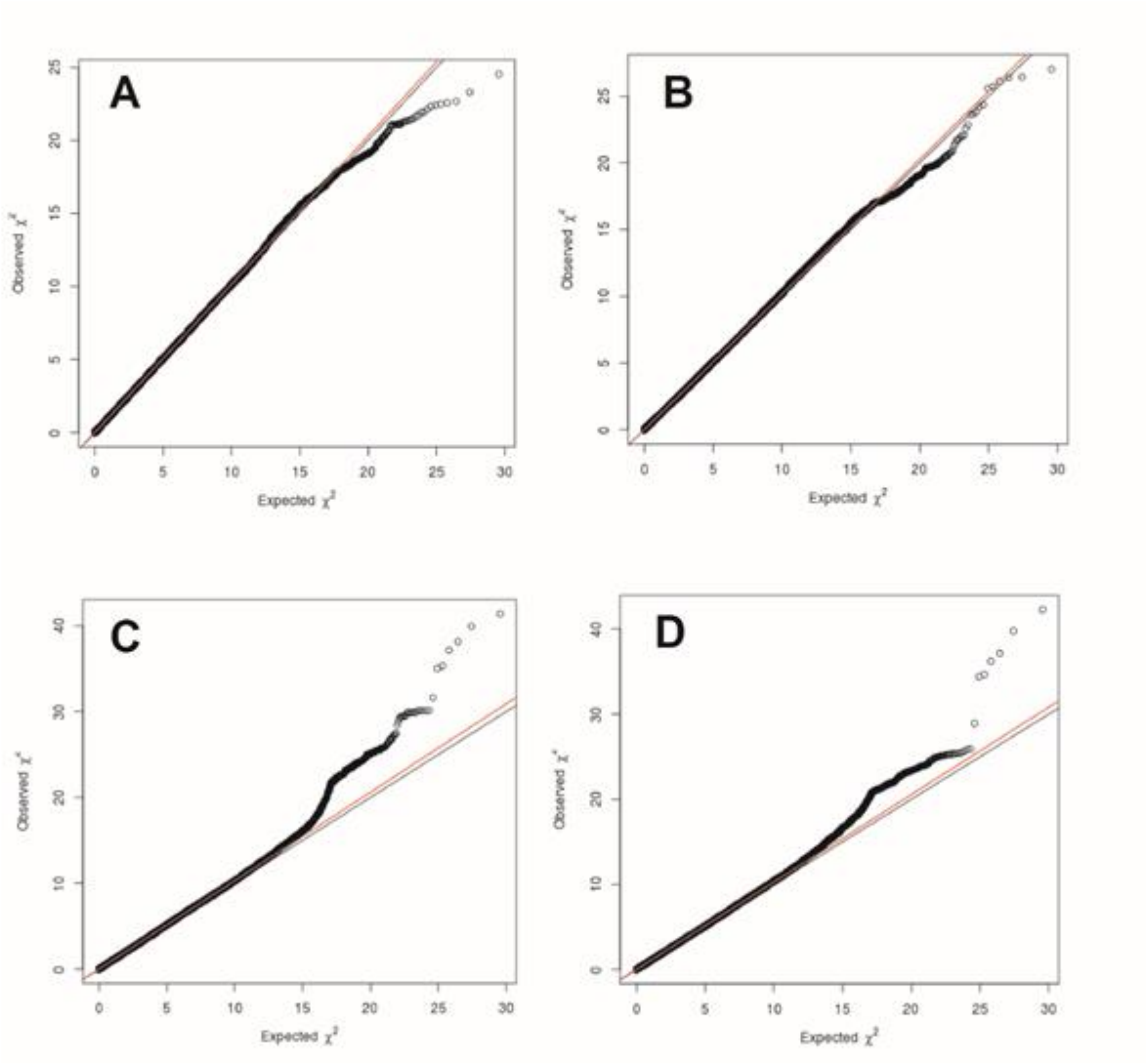


Figure E1 Quantile-quantile plot at meta-analysis level

Quantile-quantile plot of the observed versus expected chi-square values under the null for A: DLCO; adjusted for age, sex and principle components. B: DLCO; adjusted for age, sex, weight, height, smoking, and principle components. C: DLCO/VA; adjusted for age, sex and principle components. D: DLCO/VA; adjusted for age, sex, weight, height, smoking, and principle components.

Table E1 Main results of the meta-analysis in the Rotterdam Study (RS)
with N=2,574 and P-value < 5×10-6

Trait_Model	Marker Name	A1	A2	Effect	SE	P-value	Chr	Pos
DLCO_model1	**rs7092290**	c	g	0.322	0.055	**4.77E-09**	10	127968283
	10-127968301	a	aaac	-0.297	0.055	**5.33E-08**	10	127968301
	10-127968302	a	aac	-0.296	0.055	**7.49E-08**	10	127968302
	rs3858318	a	g	-0.295	0.055	**9.29E-08**	10	127969267
	rs6597758	t	c	-0.292	0.056	1.42E-07	10	127964993
	rs6597757	c	g	0.285	0.057	5.19E-07	10	127964653
	rs7072808	t	c	0.283	0.057	6.08E-07	10	127964149
	rs2886736	a	g	0.278	0.056	6.38E-07	10	127974346
	rs182670994	a	c	3.379	0.682	7.33E-07	9	86169609
	rs61773616	t	g	-0.734	0.149	8.42E-07	1	73553643
	rs61767582	t	c	-0.722	0.146	8.59E-07	1	73586252
	rs11816765	t	c	0.270	0.055	9.23E-07	10	127973248
	rs7083626	a	c	-0.261	0.053	9.97E-07	10	127975022
DLCO_model2	12-69994371	ct	c	0.191	0.037	1.78E-07	12	69994371
	rs190691083	c	g	0.713	0.137	2.01E-07	22	42946620
	rs7092290	c	g	0.259	0.050	2.51E-07	10	127968283
	rs502736	a	g	0.178	0.035	3.32E-07	12	69922738
	rs710761	c	g	-0.184	0.036	3.80E-07	12	69997061
	rs149201752	c	g	-2.046	0.404	3.95E-07	1	234292220
	rs115748414	a	g	-0.674	0.133	4.40E-07	5	108757118
	rs710763	t	g	-0.182	0.036	4.51E-07	12	69995804
	rs710768	a	t	-0.182	0.036	4.54E-07	12	69990451
	12-70001814	a	aagtc	-0.176	0.035	4.89E-07	12	70001814
	rs485288	a	g	-0.182	0.036	5.09E-07	12	69980028
	rs61929307	T	g	0.175	0.035	5.81E-07	12	69997422
	rs484319	C	g	-0.181	0.036	5.83E-07	12	69980141
	rs710760	A	t	0.181	0.036	5.91E-07	12	69997067
	rs710770	T	c	-0.180	0.036	6.35E-07	12	69989730
	rs710773	A	g	-0.181	0.037	6.76E-07	12	69987494
	rs550295	A	g	-0.180	0.036	6.87E-07	12	69947351
	rs528034	A	g	-0.178	0.036	7.01E-07	12	69938534
	rs39679	A	g	0.178	0.036	8.47E-07	12	70002265
	rs74426828	T	c	-0.648	0.132	9.07E-07	5	108722192
	rs114218475	T	c	0.620	0.126	9.21E-07	5	108785530
	rs710772	A	g	-0.179	0.036	9.70E-07	12	69987968
DLCO/VA_model1	-	-	-	-	-	-	-	-
DLCO/VA_model2	rs146224372	A	g	0.263	0.050	1.74E-07	10	87181273
	rs116995423	C	g	-0.138	0.027	4.77E-07	21	24371855
	rs12810179	A	c	0.033	0.007	6.08E-07	12	69172051
	rs11939458	T	g	-0.047	0.0096	8.61E-07	4	126268477
	rs75346256	C	g	0.048	0.0097	8.69E-07	4	126266377

A1: first allele; A2: second allele; Chr: chromosome; DLCO: diffusing capacity of the lung for carbon monoxide; DLCO/VA: diffusing capacity of the lung for carbon monoxide per alveolar volume; RS: the Rotterdam Study; SE: Standard error; Pos: Position.

*Model1: Adjusted for age, sex and principal components of genetic relatedness. Model2: Adjusted for age, sex, weight, height, smoking and principal components of genetic relatedness.

Table E2 Main results of the GWAS in the Framingham Heart Study (FHS) with N=5,798 and P-value < 5×10^{-6}

Trait_Model	Marker Name	A1	A2	Effect	SE	P-value	Chr	Pos
DLCO_model1	-	-	-	-	-	-	-	-
DLCO_model2	rs61779154	A	G	0.636	0.128	6.73E-07	1	40861949
	rs61779153	C	T	0.617	0.126	9.45E-07	1	40861748
DLCO/VA_model1	**rs17280293**	A	G	-0.076	0.013	**6.69E-09**	6	142688969
	rs9403386	A	C	-0.076	0.014	**3.17E-08**	6	142764073
	rs9403391	C	T	-0.067	0.012	7.02E-08	6	142814991
	rs148274477	C	T	-0.074	0.014	9.71E-08	6	142838173
	rs73780219	G	A	-0.066	0.013	1.41E-07	6	142722866
	rs56315120	G	A	0.058	0.011	1.49E-07	1	165168869
	rs73780221	G	C	-0.066	0.013	1.64E-07	6	142725182
	rs73840498	G	A	-0.105	0.021	5.83E-07	4	112207301
	rs16840542	T	C	0.044	0.009	7.74E-07	1	165143224
	rs72700479	C	T	0.043	0.009	8.40E-07	1	165136095
	rs2027573	C	T	0.043	0.009	8.51E-07	1	165137813
DLCO/VA_model2	**rs17280293**	A	G	-0.073	0.012	**2.32E-09**	6	142688969
	rs9403386	A	C	-0.070	0.013	**2.99E-08**	6	142764073
	rs9403391	C	T	-0.063	0.012	5.28E-08	6	142814991
	rs148274477	C	T	-0.070	0.013	6.06E-08	6	142838173
	rs73780219	G	A	-0.062	0.012	1.35E-07	6	142722866
	rs73780221	G	C	-0.062	0.011	1.53E-07	6	142725182
	rs73840498	G	A	-0.101	0.020	2.12E-07	4	112207301
	rs55861520	C	T	-0.101	0.020	6.94E-07	16	77518045
	rs79173154	T	A	0.064	0.013	7.39E-07	4	30664918
	16-83781200	R	D	-0.039	0.009	8.84E-07	16	83781200

A1: first allele; A2: second allele; Chr: chromosome; DLCO: diffusing capacity of the lung for carbon monoxide; DLCO/VA: diffusing capacity of the lung for carbon monoxide per alveolar volume; FHS: Framingham Heart Study; SE: Standard error; Pos: Position.

*Model1: Adjusted for age, sex and principal components of genetic relatedness. Model2: Adjusted for age, sex, weight, height, smoking and principal components of genetic relatedness.

Table E3 Results of the meta-analysis in both cohorts; the Rotterdam Study and the Framingham Heart Study

with N=8,372 and P-value < 5×10-6

Trait_Model	Marker Name	A1	A2	Effect	SE	P-value	Chr	Pos
DLCO_model1	-	-	-	-	-	-	-	-
DLCO_model2	rs1665696	t	c	0.10	2.07E-02	8.66E-07	10	73423190
	rs1665631	a	g	0.10	2.06E-02	7.99E-07	10	73427057
	rs1665630	t	c	0.11	2.07E-02	2.78E-07	10	73426862
	rs2423124	t	c	-0.16	3.10E-02	4.24E-07	20	5636945
	rs1665698	t	g	-0.11	2.10E-02	3.22E-07	10	73424602
	rs1665627	a	g	0.11	2.07E-02	2.73E-07	10	73425183
DLCO/VA_model1	rs12197866	t	c	0.02	4.60E-03	5.13E-07	6	142706063
	rs4700499	t	c	0.02	3.90E-03	3.40E-07	5	61938132
	rs6900087	a	t	-0.02	4.60E-03	4.19E-07	6	142717303
	rs7776356	a	g	-0.02	4.50E-03	3.31E-08	6	142777029
	rs6570509	t	g	0.02	4.00E-03	8.14E-07	6	142716286
	rs34018047	c	g	0.02	4.50E-03	5.58E-08	6	142790873
	rs7706610	t	c	0.02	3.90E-03	4.79E-07	5	61914033
	5-61756094	ctt	c	-0.02	3.90E-03	9.86E-07	5	61756094
	5-61594998	t	tttaa	0.02	3.90E-03	9.43E-07	5	61594998
	rs7735741	t	c	0.02	3.90E-03	4.03E-07	5	61930099
	rs3817928	a	g	-0.02	4.60E-03	2.02E-07	6	142750516
	rs9389994	t	c	0.02	4.00E-03	7.33E-07	6	142789158
	rs13198644	a	g	-0.02	4.50E-03	3.93E-08	6	142783233
	rs11759653	a	g	0.02	4.60E-03	4.05E-07	6	142720354
	rs12189838	a	g	-0.02	4.50E-03	4.12E-08	6	142768817
	rs7754638	a	t	-0.02	4.00E-03	6.33E-07	6	142780251
	rs76308788	t	c	-0.04	8.50E-03	6.63E-07	4	5231286
	rs10044843	a	g	-0.02	3.80E-03	8.80E-07	5	61606371
	rs6903424	a	c	-0.02	4.60E-03	5.52E-07	6	142699948
	rs4700004	a	c	-0.02	4.10E-03	5.76E-07	5	61560978
	rs1329707	t	c	-0.02	4.60E-03	3.41E-07	6	142724439
	rs262118	a	c	0.02	4.70E-03	7.08E-07	6	142843054
	rs171891	a	g	0.02	4.80E-03	6.56E-07	6	142850612
	rs10054305	a	g	0.02	3.70E-03	8.69E-07	5	61899148
	rs9403389	t	c	0.02	4.80E-03	7.76E-07	6	142789241
	rs4700501	a	g	-0.02	4.00E-03	2.79E-07	5	61953289
	rs10053650	a	t	0.02	3.90E-03	2.47E-07	5	61938896
	rs4637667	a	c	0.02	4.00E-03	8.86E-07	6	142794021
	rs7729526	t	g	-0.02	3.70E-03	8.55E-07	5	61907478
	rs7735107	t	g	0.02	3.90E-03	3.40E-07	5	61929719
	rs3817929	c	g	0.02	3.90E-03	5.69E-07	6	142751062
	rs6922607	a	g	-0.02	4.60E-03	8.63E-07	6	142703483
	rs7717128	a	g	-0.02	3.70E-03	8.52E-07	5	61894829
	rs2344396	a	g	0.02	3.80E-03	9.73E-07	5	61605567
	rs2112884	a	c	-0.02	4.10E-03	8.39E-07	5	61551997
	rs1040526	a	g	-0.02	4.00E-03	6.18E-07	6	142735816
	rs262113	t	g	-0.02	4.60E-03	8.86E-08	6	142824950
	rs9373346	a	g	0.02	3.90E-03	5.08E-07	6	142746992
	rs1862569	t	c	0.02	3.90E-03	3.25E-07	5	61928513
	rs12521329	t	c	0.02	3.90E-03	4.04E-07	5	61921815

	6-142781102	a	attaag	-0.02	4.40E-03	7.96E-08	6	142781102
	5-61920308	t	tgag	0.02	3.90E-03	2.67E-07	5	61920308
	rs6937121	t	g	-0.02	3.90E-03	7.95E-07	6	142707133
	rs4304190	a	g	-0.02	4.50E-03	3.73E-08	6	142778912
	rs9496374	c	g	0.02	4.00E-03	6.04E-07	6	142735221
	rs1329705	a	g	0.02	4.60E-03	1.78E-07	6	142753338
	rs12664563	a	g	-0.02	4.50E-03	4.06E-08	6	142785201
	rs10071568	a	c	-0.02	3.70E-03	9.45E-07	5	61900149
	rs611802	a	c	-0.02	4.00E-03	6.92E-07	6	142866387
	rs4700498	a	g	0.02	3.90E-03	5.11E-07	5	61937729
	rs2294771	t	g	-0.02	4.00E-03	8.90E-07	6	142760962
	rs10051610	t	c	0.02	3.90E-03	3.26E-07	5	61931163
	rs73780221	c	g	0.06	1.08E-02	3.06E-09	6	142725182
	rs11155242	a	c	-0.02	4.60E-03	4.25E-07	6	142691549
	rs6570511	a	g	0.02	4.50E-03	8.00E-08	6	142757368
	rs6888641	a	g	0.02	3.70E-03	5.89E-07	5	61920041
	rs1541677	a	c	-0.02	3.70E-03	5.86E-07	5	61931563
	5-61594993	t	tttta	0.02	3.90E-03	7.69E-07	5	61594993
	rs6900233	c	g	-0.02	4.60E-03	3.71E-07	6	142717283
	rs13185924	c	g	-0.02	3.90E-03	5.51E-07	5	61920705
	rs10471545	a	g	0.02	3.80E-03	9.69E-07	5	61607268
	rs7757571	a	c	-0.02	4.60E-03	5.04E-07	6	142702589
	rs962554	t	c	-0.02	4.00E-03	4.11E-07	6	142734204
	rs1040525	t	c	0.02	4.00E-03	9.20E-07	6	142703669
	rs7709562	a	c	-0.02	3.90E-03	3.24E-07	5	61928585
	6-142704139	g	gt	-0.02	4.60E-03	8.32E-07	6	142704139
	rs10072795	t	c	0.02	3.70E-03	7.10E-07	5	61926737
	rs12213892	a	g	-0.02	4.60E-03	5.17E-07	6	142702234
	rs10078786	t	c	0.02	3.90E-03	3.10E-07	5	61940050
	rs148274477	t	c	0.08	1.22E-02	2.45E-10	6	142838173
	rs262117	a	g	0.03	4.50E-03	2.01E-08	6	142807093
	rs6901807	t	g	0.02	4.50E-03	3.57E-08	6	142772228
	6-142830404	a	at	0.02	4.80E-03	3.03E-07	6	142830404
	rs2112982	t	c	0.02	3.90E-03	3.26E-07	5	61939973
	rs6906468	t	c	-0.02	4.50E-03	3.03E-08	6	142769386
	rs6929442	t	c	-0.02	3.90E-03	6.31E-07	6	142742659
	rs7765770	t	c	0.02	4.60E-03	4.57E-07	6	142687305
	rs56315120	a	g	-0.05	9.30E-03	7.78E-07	1	165168869
	rs13167856	a	t	-0.02	3.90E-03	3.96E-07	5	61920662
	rs262130	t	c	0.02	4.60E-03	1.73E-07	6	142853486
	rs918606	a	g	-0.02	3.80E-03	5.96E-08	5	61926379
	rs73780219	a	g	0.06	1.07E-02	2.51E-09	6	142722866
	rs3748069	a	g	-0.02	4.00E-03	5.34E-07	6	142767633
	rs2294775	c	g	-0.02	4.50E-03	3.39E-08	6	142766347
	rs984932	t	c	0.02	4.40E-03	4.41E-07	6	142803037
	rs12190271	a	g	0.02	4.60E-03	6.18E-07	6	142681409
	rs13159750	t	c	0.02	3.80E-03	8.62E-07	5	61600316
	rs7776375	a	g	-0.02	4.00E-03	6.46E-07	6	142777064
	rs262124	a	t	-0.02	4.00E-03	7.77E-07	6	142838617
	rs10051492	a	g	-0.02	3.80E-03	5.51E-07	5	61909886
	5-61837343	ca	c	0.02	3.90E-03	9.45E-07	5	61837343
	rs9403387	t	g	0.02	4.00E-03	6.04E-07	6	142773210
	rs77224873	a	g	-0.04	8.40E-03	7.70E-07	4	5229518
	rs6912639	t	c	-0.02	4.50E-03	3.06E-08	6	142770548

	rs4700012	a	g	-0.02	3.80E-03	6.36E-07	5	61906199
	rs9403386	a	c	-0.07	1.15E-02	1.17E-09	6	142764073
	rs4037273	t	c	0.02	4.20E-03	8.27E-07	5	61549376
	rs17071756	t	c	-0.02	4.60E-03	5.96E-07	6	142715195
	rs10065349	t	c	0.02	3.90E-03	5.36E-07	5	61912288
	rs262125	a	t	-0.03	4.70E-03	5.22E-08	6	142838355
	rs17280293	a	g	-0.07	1.13E-02	1.41E-10	6	142688969
	rs9496369	t	c	0.02	4.00E-03	9.03E-07	6	142724918
	rs9403391	t	c	0.07	1.08E-02	5.73E-10	6	142814991
	rs6449601	a	g	-0.02	3.70E-03	4.46E-07	5	61916333
	rs10484733	c	g	-0.02	4.60E-03	5.28E-07	6	142710988
	rs9291756	a	g	-0.02	4.10E-03	6.46E-07	5	61559700
	rs13192074	a	g	0.03	6.00E-03	4.69E-08	6	142834078
	6-142738314	cttctt	c	-0.02	4.60E-03	3.12E-07	6	142738314
	rs3846466	t	c	0.02	4.10E-03	9.28E-07	5	61558172
	rs643975	c	g	-0.02	4.60E-03	1.80E-07	6	142844251
	rs40110	a	g	0.02	3.70E-03	8.87E-07	5	61763852
	rs2294764	a	g	0.02	4.00E-03	5.60E-07	6	142737504
	rs1928528	t	g	-0.02	4.50E-03	3.74E-08	6	142779109
	rs4290970	t	c	0.02	3.90E-03	9.94E-07	5	61602661
	rs9373347	t	c	0.02	4.40E-03	7.84E-08	6	142779885
	6-142738312	ctct	c	-0.02	5.00E-03	9.08E-07	6	142738312
	rs75834976	a	c	-0.04	8.40E-03	6.03E-07	4	5231710
	rs7718484	t	c	-0.02	3.80E-03	5.08E-07	5	61912713
	rs26631	t	c	-0.02	3.80E-03	9.61E-07	5	61768423
	rs13176954	c	g	-0.02	3.90E-03	2.29E-07	5	61941491
	rs12516160	a	t	0.02	3.80E-03	6.98E-07	5	61900784
	6-142781103	t	ttaagg	-0.02	4.60E-03	1.88E-07	6	142781103
	rs262120	a	c	0.02	4.60E-03	1.78E-07	6	142842360
	rs7756434	a	g	-0.02	4.50E-03	3.31E-08	6	142775295
	rs1360194	a	g	0.02	3.90E-03	5.87E-07	6	142752595
	rs7755109	a	g	-0.02	3.90E-03	6.23E-07	6	142750392
DLCO/VA_model2	rs4700499	t	c	0.02	3.60E-03	5.41E-07	5	61938132
	rs7776356	a	g	-0.02	4.20E-03	4.80E-07	6	142777029
	rs34018047	c	g	0.02	4.20E-03	6.89E-07	6	142790873
	rs7706610	t	c	0.02	3.60E-03	8.60E-07	5	61914033
	rs7735741	t	c	0.02	3.60E-03	7.34E-07	5	61930099
	rs13198644	a	g	-0.02	4.20E-03	5.53E-07	6	142783233
	rs12189838	a	g	-0.02	4.20E-03	7.34E-07	6	142768817
	rs4700004	a	c	-0.02	3.80E-03	9.37E-07	5	61560978
	rs4700501	a	g	-0.02	3.80E-03	6.22E-07	5	61953289
	rs10053650	a	t	0.02	3.60E-03	4.87E-07	5	61938896
	rs7735107	t	g	0.02	3.60E-03	6.03E-07	5	61929719
	rs262113	t	g	-0.02	4.30E-03	5.00E-07	6	142824950
	rs9373346	a	g	0.02	3.70E-03	9.96E-07	6	142746992
	rs1862569	t	c	0.02	3.60E-03	6.15E-07	5	61928513
	rs12521329	t	c	0.02	3.60E-03	7.19E-07	5	61921815
	5-61920308	t	tgag	0.02	3.70E-03	5.74E-07	5	61920308
	rs4304190	a	g	-0.02	4.20E-03	5.32E-07	6	142778912
	rs9496374	c	g	0.02	3.70E-03	9.90E-07	6	142735221
	rs12664563	a	g	-0.02	4.20E-03	5.64E-07	6	142785201
	rs611802	a	c	-0.02	3.80E-03	8.72E-07	6	142866387
	rs10051610	t	c	0.02	3.60E-03	5.74E-07	5	61931163

	rs73780221	c	g	0.06	1.01E-02	4.44E-09	6	142725182
	rs962554	t	c	-0.02	3.70E-03	8.32E-07	6	142734204
	rs7709562	a	c	-0.02	3.60E-03	6.13E-07	5	61928585
	rs10078786	t	c	0.02	3.60E-03	4.95E-07	5	61940050
	rs148274477	t	c	0.07	1.14E-02	2.85E-10	6	142838173
	rs262117	a	g	0.02	4.20E-03	3.62E-07	6	142807093
	rs6901807	t	g	0.02	4.20E-03	4.43E-07	6	142772228
	rs2112982	t	c	0.02	3.60E-03	5.15E-07	5	61939973
	rs6906468	t	c	-0.02	4.20E-03	4.64E-07	6	142769386
	rs13167856	a	t	-0.02	3.60E-03	7.07E-07	5	61920662
	rs262130	t	c	0.02	4.30E-03	9.28E-07	6	142853486
	rs918606	a	g	-0.02	3.60E-03	7.49E-08	5	61926379
	rs73780219	a	g	0.06	1.00E-02	3.92E-09	6	142722866
	rs2294775	c	g	-0.02	4.20E-03	4.08E-07	6	142766347
	rs10051492	a	g	-0.02	3.60E-03	9.81E-07	5	61909886
	rs6912639	t	c	-0.02	4.20E-03	4.66E-07	6	142770548
	rs9403386	a	c	-0.06	1.08E-02	1.77E-09	6	142764073
	rs262125	a	t	-0.02	4.40E-03	3.58E-07	6	142838355
	rs17280293	a	g	-0.07	1.06E-02	7.85E-11	6	142688969
	rs9403391	t	c	0.06	1.01E-02	1.09E-09	6	142814991
	rs643975	c	g	-0.02	4.30E-03	9.89E-07	6	142844251
	rs1928528	t	g	-0.02	4.20E-03	5.33E-07	6	142779109
	rs7718484	t	c	-0.02	3.60E-03	9.03E-07	5	61912713
	rs13176954	c	g	-0.02	3.60E-03	4.52E-07	5	61941491
	rs262120	a	c	0.02	4.30E-03	9.82E-07	6	142842360
	rs7756434	a	g	-0.02	4.20E-03	4.86E-07	6	142775295

A1: first allele; A2: second allele; Chr: chromosome; DLCO: diffusing capacity of the lung for carbon monoxide; DLCO/VA: diffusing capacity of the lung for carbon monoxide per alveolar volume; SE: Standard error; Pos: Position.

*Model1: Adjusted for age, sex and principal components of genetic relatedness. Model2: Adjusted for age, sex, weight, height, smoking and principal components of genetic relatedness.

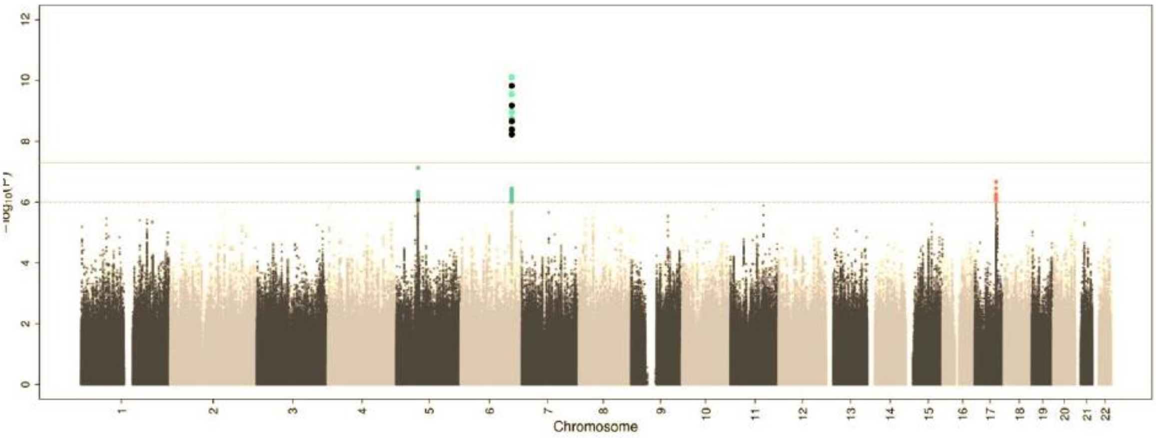


Figure E2 Double Manhattan-plot where results of the meta-analysis of DLCO/VA before and after adjustment with FEV_1/FVC in model 2.

For variants with P-value lower than 5×10^{-6}, the blue colour represents a more significant association before adjustment compared to the black dots below which represent the same associations with a less significant P-value after adjustment with FEV_1/FVC. The red colour represents a more significant association after adjustment with FEV_1/FVC compared to the black dots below which represent the same associations with a less significant p-value before adjustment with FEV_1/FVC.

Model 2: Adjusted for age, sex, weight, height, smoking and principal components of genetic relatedness.

Table E4 Overlap with reported COPD-associated variants and those associated with DLCO in Model 1

Marker Name	A1	A2	Effect	SE	P-value	Chr	Pos
rs9403391	t	c	0.169	0.068	0.014	6	142814991
rs17486278	a	c	0.056	0.025	0.022	15	78867482
rs11853359	a	g	-0.054	0.024	0.025	15	71621524
rs1441358	t	g	0.052	0.024	0.031	15	71612514
rs72811310	t	g	-0.073	0.036	0.044	5	156948318
rs10815649	t	c	0.055	0.028	0.051	9	7620482
rs4742382	a	g	0.054	0.028	0.056	9	7620040
rs647097	t	c	0.048	0.025	0.058	18	8808464
rs2415116	t	c	-0.050	0.027	0.068	15	71673185
rs754388	c	g	-0.053	0.032	0.090	14	93115410
rs2076295	t	g	0.035	0.023	0.131	6	7563232
rs4597955	a	g	-0.040	0.027	0.136	5	147847273
rs631126	t	c	-0.039	0.027	0.145	18	8800723
rs2806356	t	c	-0.043	0.029	0.145	6	109266255
rs16891339	a	g	0.092	0.066	0.163	6	80647622
rs78242330	t	c	-0.068	0.052	0.192	14	93111715
rs7733401	a	c	-0.032	0.026	0.228	5	147833281
rs6058526	a	g	-0.040	0.034	0.235	20	30699632
rs36110266	a	g	0.040	0.034	0.235	20	30695031
rs2034241	a	g	0.035	0.029	0.236	5	65085330
rs6908022	a	t	0.046	0.041	0.262	6	96480212
rs10429950	t	c	-0.027	0.026	0.294	1	218624533
rs4904964	a	c	-0.027	0.026	0.300	14	93099867
rs4846479	t	g	0.026	0.026	0.309	1	218598410
rs11168048	t	c	0.023	0.024	0.331	5	147842353
rs7727161	t	g	-0.025	0.026	0.335	5	147832486
rs60708069	t	g	-0.030	0.033	0.354	5	147837664
rs7733088	a	g	-0.023	0.026	0.369	5	147856333
rs11628180	a	g	0.024	0.027	0.370	14	93068516
rs55724484	a	g	0.022	0.025	0.371	3	75380823
rs11905172	t	c	-0.027	0.032	0.393	20	30797628
rs16825267	c	g	0.035	0.045	0.430	2	229569919
rs13192074	a	g	0.030	0.038	0.432	6	142834078
rs2843016	a	g	-0.020	0.026	0.434	1	120322961
rs13141641	t	c	0.018	0.024	0.461	4	145506456
rs1435867	t	c	0.035	0.048	0.463	2	229510929
rs2955083	a	t	0.026	0.036	0.464	3	127961178
rs6087358	a	g	0.025	0.035	0.464	20	30855746
rs113554904	a	g	0.019	0.027	0.466	3	188483788
rs17707300	t	c	-0.017	0.024	0.475	16	28593347
rs56168343	t	c	-0.022	0.031	0.475	5	156928008
rs1737890	t	g	0.024	0.034	0.477	20	31042595
rs9399401	t	c	-0.018	0.026	0.479	6	142668901

rs2999090	a	g	0.025	0.036	0.489	3	127931340
rs7937	t	c	-0.016	0.024	0.497	19	41302706
rs2582790	a	c	-0.017	0.025	0.502	1	120314849
rs2039987	a	c	-0.017	0.026	0.506	6	142655490
rs7186831	a	g	0.019	0.029	0.512	16	75473155
rs6837671	a	g	0.015	0.024	0.527	4	89873092
rs9396712	t	c	0.016	0.026	0.547	6	16818625
rs13080090	t	g	0.021	0.036	0.567	3	171974838
rs56308303	t	c	0.013	0.024	0.569	15	71669872
rs185212652	a	t	-0.019	0.035	0.575	5	147837533
rs112458284	t	c	-0.049	0.089	0.582	14	94672731
rs11904894	t	c	-0.014	0.026	0.584	20	19056247
rs721917	a	g	-0.013	0.023	0.584	10	81706324
rs75720504	a	c	0.022	0.047	0.643	5	156935973
rs12435118	t	c	0.016	0.036	0.653	14	102673993
rs6573633	a	g	-0.010	0.023	0.656	14	66272664
rs3782563	a	g	-0.010	0.024	0.660	12	96639739
rs12459249	t	c	0.011	0.027	0.692	19	41339896
rs1265120	a	c	0.010	0.024	0.692	8	103190071
rs1265122	t	c	0.009	0.024	0.717	8	103190530
rs12189594	t	g	0.008	0.023	0.735	6	14856357
rs192394604	t	g	-0.009	0.026	0.739	8	103148763
rs1568010	t	g	0.007	0.024	0.765	15	71668512
rs17035917	t	c	-0.013	0.045	0.769	4	106520742
rs58873874	t	c	0.013	0.047	0.783	5	156945148
rs28929474	t	c	-0.023	0.090	0.796	14	94844947
rs1529672	a	c	0.008	0.031	0.803	3	25520582
rs11727735	a	g	0.005	0.045	0.904	4	106631870
rs13147502	a	g	0.002	0.024	0.950	4	106143797
rs2047409	a	g	-0.001	0.024	0.951	4	106137033

A1: first allele; A2: second allele; Chr: chromosome; DLCO: Diffusing capacity of the lung for carbon monoxide; SE: Standard error; Pos: Position.

Model1: Adjusted for age, sex and principal components of genetic relatedness.

Table E5 Overlap with reported COPD-associated variants and those associated with DLCO in Model 2

Marker Name	A1	A2	Effect	SE	P-value	Chr	Pos
rs11853359	a	g	-0.056	0.022	0.009	15	71621524
rs754388	c	g	-0.073	0.028	0.009	14	93115410
rs72811310	t	g	-0.081	0.033	0.012	5	156948318
rs9403391	t	c	0.152	0.061	0.013	6	142814991
rs1441358	t	g	0.053	0.022	0.014	15	71612514
rs10815649	t	c	0.060	0.025	0.017	9	7620482
rs4742382	a	g	0.058	0.025	0.021	9	7620040
rs17486278	a	c	0.050	0.022	0.022	15	78867482
rs78242330	t	c	-0.106	0.047	0.023	14	93111715
rs2415116	t	c	-0.049	0.024	0.045	15	71673185
rs647097	t	c	0.041	0.023	0.070	18	8808464
rs2039987	a	c	-0.040	0.023	0.078	6	142655490
rs9399401	t	c	-0.040	0.023	0.082	6	142668901
rs28929474	t	c	-0.139	0.081	0.085	14	94844947
rs631126	t	c	-0.040	0.024	0.092	18	8800723
rs55724484	a	g	0.033	0.022	0.136	3	75380823
rs4904964	a	c	-0.034	0.023	0.143	14	93099867
rs17035917	t	c	-0.059	0.041	0.148	4	106520742
rs11628180	a	g	0.034	0.024	0.166	14	93068516
rs11727735	a	g	0.055	0.040	0.171	4	106631870
rs4597955	a	g	-0.028	0.024	0.236	5	147847273
rs13141641	t	c	0.025	0.021	0.237	4	145506456
rs2076295	t	g	0.024	0.020	0.239	6	7563232
rs13192074	a	g	0.040	0.034	0.245	6	142834078
rs2034241	a	g	0.030	0.026	0.249	5	65085330
rs11904894	t	c	-0.026	0.024	0.275	20	19056247
rs7733401	a	c	-0.025	0.024	0.280	5	147833281
rs6908022	a	t	0.037	0.037	0.310	6	96480212
rs6058526	a	g	-0.031	0.030	0.311	20	30699632
rs36110266	a	g	0.031	0.030	0.312	20	30695031
rs2843016	a	g	-0.023	0.023	0.315	1	120322961
rs2582790	a	c	-0.023	0.023	0.318	1	120314849
rs12459249	t	c	0.024	0.025	0.331	19	41339896
rs11905172	t	c	-0.027	0.029	0.341	20	30797628
rs10429950	t	c	-0.021	0.023	0.354	1	218624533
rs9396712	t	c	0.021	0.023	0.360	6	16818625
rs4846479	t	g	0.021	0.023	0.373	1	218598410
rs7937	t	c	-0.019	0.021	0.375	19	41302706
rs2806356	t	c	-0.023	0.026	0.386	6	109266255
rs7727161	t	g	-0.019	0.024	0.410	5	147832486
rs1737890	t	g	0.024	0.031	0.434	20	31042595
rs56168343	t	c	-0.021	0.027	0.444	5	156928008
rs6837671	a	g	0.015	0.021	0.468	4	89873092

rs3782563	a	g	-0.015	0.021	0.486	12	96639739
rs75720504	a	c	0.029	0.042	0.494	5	156935973
rs2955083	a	t	0.022	0.032	0.495	3	127961178
rs12189594	t	g	0.014	0.021	0.495	6	14856357
rs2999090	a	g	0.021	0.032	0.509	3	127931340
rs112458284	t	c	0.051	0.079	0.521	14	94672731
rs192394604	t	g	-0.014	0.023	0.554	8	103148763
rs12435118	t	c	0.019	0.032	0.555	14	102673993
rs58873874	t	c	0.024	0.042	0.560	5	156945148
rs11168048	t	c	0.012	0.022	0.572	5	147842353
rs1529672	a	c	0.016	0.028	0.573	3	25520582
rs113554904	a	g	0.013	0.024	0.582	3	188483788
rs56308303	t	c	0.011	0.021	0.585	15	71669872
rs17707300	t	c	-0.011	0.021	0.593	16	28593347
rs7186831	a	g	0.014	0.026	0.601	16	75473155
rs721917	a	g	0.010	0.021	0.617	10	81706324
rs6087358	a	g	0.015	0.031	0.622	20	30855746
rs6573633	a	g	0.010	0.021	0.634	14	66272664
rs7733088	a	g	-0.011	0.023	0.636	5	147856333
rs60708069	t	g	-0.010	0.029	0.737	5	147837664
rs13147502	a	g	0.006	0.021	0.774	4	106143797
rs16825267	c	g	0.010	0.040	0.813	2	229569919
rs1568010	t	g	0.004	0.021	0.852	15	71668512
rs1435867	t	c	0.008	0.043	0.855	2	229510929
rs13080090	t	g	-0.006	0.032	0.866	3	171974838
rs2047409	a	g	0.003	0.021	0.876	4	106137033
rs185212652	a	t	-0.004	0.031	0.888	5	147837533
rs16891339	a	g	0.008	0.059	0.889	6	80647622
rs1265122	t	c	0.003	0.022	0.899	8	103190530
rs1265120	a	c	0.003	0.021	0.903	8	103190071

A1: first allele; A2: second allele; Chr: chromosome; DLCO: Diffusing capacity of the lung for carbon monoxide; SE: Standard error; Pos: Position.

* Model2: Adjusted for age, sex, weight, height, smoking and principal components of genetic relatedness.

Table E6 Overlap with reported COPD-associated variants and those associated with DLCO/VA in Model 1

Marker Name	A1	A2	Effect	SE	P-value	Chr	Pos
rs9403391	t	c	0.067	0.011	5.73E-10	6	142814991
rs13192074	a	g	0.033	0.006	4.69E-08	6	142834078
rs11853359	a	g	-0.017	0.004	1.01E-05	15	71621524
rs9399401	t	c	-0.018	0.004	1.06E-05	6	142668901
rs2039987	a	c	-0.018	0.004	1.64E-05	6	142655490
rs1441358	t	g	0.016	0.004	3.37E-05	15	71612514
rs2415116	t	c	-0.016	0.004	2,20E-04	15	71673185
rs17486278	a	c	0.012	0.004	0.0028	15	78867482
rs112458284	t	c	0.036	0.014	0.010	14	94672731
rs72811310	t	g	-0.015	0.006	0.011	5	156948318
rs28929474	t	c	-0.035	0.014	0.015	14	94844947
rs55724484	a	g	0.009	0.004	0.028	3	75380823
rs11905172	t	c	-0.010	0.005	0.049	20	30797628
rs2955083	a	t	0.011	0.006	0.059	3	127961178
rs2999090	a	g	0.011	0.006	0.064	3	127931340
rs17707300	t	c	-0.007	0.004	0.080	16	28593347
rs56308303	t	c	0.007	0.004	0.080	15	71669872
rs6837671	a	g	0.006	0.004	0.093	4	89873092
rs11727735	a	g	0.011	0.007	0.109	4	106631870
rs13080090	t	g	0.009	0.006	0.110	3	171974838
rs2034241	a	g	0.007	0.005	0.121	5	65085330
rs36110266	a	g	0.008	0.005	0.128	20	30695031
rs7937	t	c	0.006	0.004	0.130	19	41302706
rs6058526	a	g	-0.008	0.005	0.132	20	30699632
rs6087358	a	g	0.008	0.006	0.171	20	30855746
rs6573633	a	g	-0.005	0.004	0.180	14	66272664
rs17035917	t	c	-0.009	0.007	0.208	4	106520742
rs1568010	t	g	0.004	0.004	0.259	15	71668512
rs10815649	t	c	0.005	0.005	0.266	9	7620482
rs1737890	t	g	0.006	0.006	0.279	20	31042595
rs4742382	a	g	0.005	0.005	0.283	9	7620040
rs1529672	a	c	0.005	0.005	0.296	3	25520582
rs6908022	a	t	0.007	0.007	0.308	6	96480212
rs2076295	t	g	-0.004	0.004	0.326	6	7563232
rs12189594	t	g	0.003	0.004	0.367	6	14856357
rs2806356	t	c	-0.004	0.005	0.369	6	109266255
rs7186831	a	g	-0.004	0.005	0.379	16	75473155
rs7733088	a	g	0.003	0.004	0.412	5	147856333
rs58873874	t	c	-0.006	0.007	0.413	5	156945148
rs75720504	a	c	-0.006	0.007	0.417	5	156935973
rs721917	a	g	-0.003	0.004	0.437	10	81706324
rs11904894	t	c	0.003	0.004	0.454	20	19056247
rs4904964	a	c	0.003	0.004	0.460	14	93099867

rs185212652	a	t	0.004	0.006	0.479	5	147837533
rs113554904	a	g	0.003	0.004	0.497	3	188483788
rs2582790	a	c	0.003	0.004	0.503	1	120314849
rs13141641	t	c	-0.002	0.004	0.519	4	145506456
rs60708069	t	g	0.003	0.005	0.534	5	147837664
rs11168048	t	c	-0.002	0.004	0.540	5	147842353
rs2843016	a	g	0.003	0.004	0.550	1	120322961
rs12435118	t	c	-0.003	0.006	0.551	14	102673993
rs754388	c	g	0.003	0.005	0.578	14	93115410
rs1435867	t	c	0.004	0.008	0.608	2	229510929
rs56168343	t	c	0.002	0.005	0.614	5	156928008
rs1265120	a	c	-0.002	0.004	0.618	8	103190071
rs16825267	c	g	0.003	0.007	0.656	2	229569919
rs12459249	t	c	-0.002	0.004	0.657	19	41339896
rs16891339	a	g	0.005	0.011	0.666	6	80647622
rs9396712	t	c	0.002	0.004	0.685	6	16818625
rs11628180	a	g	-0.002	0.004	0.694	14	93068516
rs1265122	t	c	-0.001	0.004	0.708	8	103190530
rs3782563	a	g	-0.001	0.004	0.794	12	96639739
rs78242330	t	c	0.002	0.008	0.800	14	93111715
rs10429950	t	c	0.001	0.004	0.828	1	218624533
rs4846479	t	g	-0.001	0.004	0.841	1	218598410
rs192394604	t	g	0.001	0.004	0.868	8	103148763
rs2047409	a	g	-0.001	0.004	0.887	4	106137033
rs7733401	a	c	-0.001	0.004	0.892	5	147833281
rs4597955	a	g	-0.001	0.004	0.895	5	147847273
rs647097	t	c	0.001	0.004	0.901	18	8808464
rs13147502	a	g	0.000	0.004	0.935	4	106143797
rs7727161	t	g	0.000	0.004	0.945	5	147832486
rs631126	t	c	0.000	0.004	0.966	18	8800723

A1: first allele; A2: second allele; Chr: chromosome; DLCO/VA: Diffusing capacity of the lung for carbon monoxide by alveolar volume; SE: Standard error; Pos: Position.

Model1: Adjusted for age, sex and principal components of genetic relatedness.

Bold indicates statistical significance.

Table E7 Overlap with reported COPD-associated variants and those associated with DLCO/VA in Model 2

Marker Name	A1	A2	Effect	SE	P-value	Chr	Pos
rs9403391	t	c	0.061	0.010	1.09E-09	6	142814991
rs13192074	a	g	0.027	0.006	1.27E-06	6	142834078
rs11853359	a	g	-0.016	0.004	5.40E-06	15	71621524
rs9399401	t	c	-0.017	0.004	1.11E-05	6	142668901
rs2039987	a	c	-0.017	0.004	1.34E-05	6	142655490
rs1441358	t	g	0.015	0.004	1.73E-05	15	71612514
rs2415116	t	c	-0.014	0.004	5.76E-04	15	71673185
rs72811310	t	g	-0.015	0.005	5.88E-03	5	156948318
rs28929474	t	c	-0.034	0.013	0.011	14	94844947
rs112458284	t	c	0.031	0.013	0.018	14	94672731
rs17486278	a	c	0.008	0.004	0.020	15	78867482
rs11727735	a	g	0.015	0.007	0.024	4	106631870
rs17035917	t	c	-0.014	0.007	0.034	4	106520742
rs11905172	t	c	-0.010	0.005	0.036	20	30797628
rs55724484	a	g	0.007	0.004	0.049	3	75380823
rs56308303	t	c	0.007	0.004	0.060	15	71669872
rs6837671	a	g	0.007	0.004	0.063	4	89873092
rs7733088	a	g	0.006	0.004	0.116	5	147856333
rs36110266	a	g	0.008	0.005	0.117	20	30695031
rs6058526	a	g	-0.008	0.005	0.120	20	30699632
rs2034241	a	g	0.006	0.004	0.148	5	65085330
rs1568010	t	g	0.005	0.004	0.154	15	71668512
rs2955083	a	t	0.007	0.005	0.165	3	127961178
rs17707300	t	c	-0.005	0.004	0.165	16	28593347
rs185212652	a	t	0.007	0.005	0.168	5	147837533
rs11168048	t	c	-0.005	0.004	0.170	5	147842353
rs12189594	t	g	0.005	0.003	0.172	6	14856357
rs2999090	a	g	0.007	0.005	0.175	3	127931340
rs1529672	a	c	0.006	0.005	0.198	3	25520582
rs1737890	t	g	0.006	0.005	0.220	20	31042595
rs6087358	a	g	0.006	0.005	0.230	20	30855746
rs12435118	t	c	-0.006	0.005	0.230	14	102673993
rs13080090	t	g	0.006	0.005	0.237	3	171974838
rs60708069	t	g	0.005	0.005	0.294	5	147837664
rs7937	t	c	0.004	0.004	0.301	19	41302706
rs10815649	t	c	0.004	0.004	0.343	9	7620482
rs9396712	t	c	0.004	0.004	0.356	6	16818625
rs4742382	a	g	0.004	0.004	0.358	9	7620040
rs4904964	a	c	0.004	0.004	0.363	14	93099867
rs2076295	t	g	-0.003	0.003	0.391	6	7563232
rs6908022	a	t	0.005	0.006	0.392	6	96480212
rs6573633	a	g	-0.003	0.004	0.409	14	66272664
rs13141641	t	c	-0.003	0.004	0.429	4	145506456

rs647097	t	c	0.003	0.004	0.453	18	8808464
rs2806356	t	c	-0.003	0.004	0.461	6	109266255
rs11628180	a	g	-0.003	0.004	0.463	14	93068516
rs754388	c	g	0.003	0.005	0.470	14	93115410
rs10429950	t	c	-0.002	0.004	0.578	1	218624533
rs78242330	t	c	0.004	0.008	0.578	14	93111715
rs13147502	a	g	-0.002	0.004	0.583	4	106143797
rs1265120	a	c	-0.002	0.004	0.602	8	103190071
rs4846479	t	g	0.002	0.004	0.604	1	218598410
rs2047409	a	g	-0.002	0.004	0.608	4	106137033
rs7186831	a	g	-0.002	0.004	0.634	16	75473155
rs58873874	t	c	-0.003	0.007	0.636	5	156945148
rs631126	t	c	-0.002	0.004	0.662	18	8800723
rs75720504	a	c	-0.003	0.007	0.683	5	156935973
rs1265122	t	c	-0.001	0.004	0.698	8	103190530
rs11904894	t	c	0.002	0.004	0.710	20	19056247
rs1435867	t	c	0.002	0.007	0.739	2	229510929
rs721917	a	g	-0.001	0.003	0.760	10	81706324
rs7727161	t	g	0.001	0.004	0.766	5	147832486
rs16891339	a	g	0.002	0.010	0.810	6	80647622
rs4597955	a	g	0.001	0.004	0.814	5	147847273
rs192394604	t	g	0.001	0.004	0.821	8	103148763
rs7733401	a	c	0.001	0.004	0.828	5	147833281
rs16825267	c	g	0.001	0.007	0.872	2	229569919
rs113554904	a	g	0.000	0.004	0.914	3	188483788
rs2582790	a	c	0.000	0.004	0.916	1	120314849
rs56168343	t	c	0.000	0.005	0.940	5	156928008
rs2843016	a	g	0.000	0.004	0.969	1	120322961
rs3782563	a	g	0.000	0.004	0.974	12	96639739
rs12459249	t	c	0.000	0.004	0.989	19	41339896

A1: first allele; A2: second allele; Chr: chromosome; DLCO/VA: Diffusing capacity of the lung for carbon monoxide by alveolar volume; SE: Standard error; Pos: Position.

Model2: Adjusted for age, sex, weight, height, smoking and principal components of genetic relatedness.

Bold indicates statistical significance.

Table E8 Overlap with reported emphysema-associated variants and those associated with DLCO and DLCO/VA in the models 1 and 2

Trait_Model	Marker Name	A1	A2	Effect	SE	P-value	Chr	Pos
DLCO_model1	rs13141641	t	c	0.018	0.024	0.461	4	145506456
	rs45505795	c	g	0.028	0.085	0.742	14	94756943
	rs55676755	c	g	0.052	0.025	0.034	15	78898932
	rs142200419	t	c	0.040	0.130	0.760	4	127323308
	rs74834049	a	t	0.056	0.035	0.111	8	13029877
	rs75200691	t	g	-0.048	0.035	0.171	8	13054869
	rs55706246	a	g	0.108	0.049	0.029	21	35595637
DLCO_model2	rs13141641	t	c	0.025	0.021	0.237	4	145506456
	rs45505795	c	g	-0.052	0.076	0.493	14	94756943
	rs55676755	c	g	0.048	0.022	0.029	15	78898932
	rs142200419	t	c	0.036	0.117	0.756	4	127323308
	rs74834049	a	t	0.068	0.032	0.032	8	13029877
	rs75200691	t	g	-0.061	0.032	0.053	8	13054869
	rs55706246	a	g	0.079	0.044	0.075	21	35595637
DLCO/VA_model1	rs13141641	t	c	-0.002	0.004	0.519	4	145506456
	rs45505795	c	g	-0.029	0.014	0.031	14	94756943
	rs55676755	**c**	**g**	**0.011**	**0.004**	**0.004**	**15**	**78898932**
	rs142200419	t	c	-0.003	0.021	0.895	4	127323308
	rs74834049	a	t	0.011	0.006	0.044	8	13029877
	rs75200691	t	g	-0.010	0.006	0.068	8	13054869
	rs55706246	a	g	0.010	0.008	0.223	21	35595637
DLCO/Va_model2	rs13141641	t	c	-0.003	0.004	0.429	4	145506456
	rs45505795	c	g	-0.022	0.013	0.079	14	94756943
	rs55676755	c	g	0.008	0.004	0.026	15	78898932
	rs142200419	t	c	-0.009	0.020	0.644	4	127323308
	rs74834049	a	t	0.012	0.005	0.027	8	13029877
	rs75200691	t	g	-0.011	0.005	0.038	8	13054869
	rs55706246	a	g	0.011	0.008	0.155	21	35595637

A1: first allele; A2: second allele; Chr: chromosome; DLCO: Diffusing capacity of the lung for carbon monoxide; DLCO/VA: Diffusing capacity of the lung for carbon monoxide by alveolar volume; SE: Standard error; Pos: Position.

Model1: Adjusted for age, sex and principal components of genetic relatedness.

Model2: Adjusted for age, sex, weight, height, smoking and principal components of genetic relatedness.

Bold indicates statistical significance.

Figure E3 Haploreg analysis of the main results of the meta-analysis
[Haploreg, http://archive.broadinstitute.org/mammals/haploreg/haploreg.php]

Query SNP: rs1665630 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
10	71658698	0.86	0.93	rs1665618	G	A	0.48	0.41	0.57	0.46		ESDR	6 tissues	ESDR,ESC		4 altered motifs				CDH23	intronic
10	71658719	0.81	0.93	rs1665690	G	A	0.22	0.29	0.38	0.45		ESDR	6 tissues	ESDR,ESC		ERalpha-a,Pax-6			2 hits	CDH23	intronic
10	71659721	0.86	0.93	rs1665691	G	C	0.47	0.41	0.57	0.46			6 tissues	6 tissues		HNF1,Pbx-1,Rad21			2 hits	CDH23	intronic
10	71659823	0.81	0.93	rs1665692	G	A	0.22	0.29	0.38	0.45			6 tissues	6 tissues	MAFF,MAFK	7 altered motifs			2 hits	CDH23	intronic
10	71660471	0.82	0.93	rs1665619	T	G	0.25	0.29	0.38	0.45			4 tissues	BLD,BLD		6 altered motifs				CDH23	intronic
		0.82	0.93	rs77477177	T	C,G	0.25	0.28	0.38	0.45			ESC, IPSC, BLD	IPSC						CDH23	intronic
10	71660805	0.8	0.93	rs1665693	G	A	0.22	0.28	0.35	0.45			ESC, IPSC, BLD	IPSC		6 altered motifs				CDH23	intronic
10	71661081	0.87	0.94	rs1665622	G	A	0.23	0.29	0.38	0.46			ESC, ESDR, IPSC	ESC		Nanog				CDH23	intronic
10	71661447	0.93	0.98	rs1665623	G	A	0.27	0.39	0.56	0.48			ESC, ESDR, IPSC	4 tissues		CEBPB,CEBPD				CDH23	intronic
10	71661471	0.87	0.94	rs1665694	G	T	0.23	0.29	0.38	0.46			ESC, ESDR, IPSC	4 tissues		Ets				CDH23	intronic
10	71661491	0.93	0.98	rs1665624	T	C	0.27	0.40	0.56	0.48			ESC, ESDR, IPSC	4 tissues		5 altered motifs			2 hits	CDH23	intronic
10	71663433	0.94	1	rs1665696	C	T	0.50	0.41	0.56	0.48			5 tissues	9 tissues	CTCF	LBP-1				CDH23	intronic
10	71664845	0.93	0.97	rs1665698	T	G	0.25	0.40	0.55	0.46			IPSC, ESC, BRST		ZNF263	12 altered motifs				CDH23	intronic
10	71665426	0.98	1	rs1665627	G	A	0.28	0.41	0.56	0.47			4 tissues	ESC,IPSC,MUS		4 altered motifs				CDH23	intronic
10	71667105	1	1	rs1665630	C	T	0.39	0.41	0.56	0.47	🟪		7 tissues	7 tissues	4 bound proteins	4 altered motifs				CDH23	intronic
10	71667300	0.88	0.99	rs1665631	G	A	0.47	0.44	0.62	0.50			4 tissues	13 tissues	4 bound proteins	5 altered motifs				CDH23	intronic

Query SNP: rs2423124 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
20	5656299	1	1	rs2423124	T	C	0.75	0.70	0.67	0.79		BLD	12 tissues	6 tissues		5 altered motifs				45kb 5' of GPCPD1	

Query SNP: rs17280293 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
6	142367832	1	1	rs17280293	A	G	0.00	0.06	0.03	0.03	🟪	FAT, LNG, GI	6 tissues	12 tissues	P300	5 altered motifs				GPR126	missense
6	142401729	0.86	1	rs73780219	G	A	0.09	0.07	0.10	0.04			ESDR, GI, VAS			6 altered motifs				GPR126	intronic
6	142404045	0.89	1	rs73780221	G	C	0.09	0.07	0.10	0.04			LIV			Ascl2,PU.1				GPR126	intronic

Query SNP: rs918606 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
5	62599002	0.87	0.97	rs7717128	G	A	0.67	0.59	0.37	0.57						FXR			7 hits	IPO11	intronic
5	62603321	0.87	0.97	rs10054305	A	G	0.67	0.59	0.37	0.57						Gfi1b			7 hits	IPO11	intronic
5	62604322	0.86	0.97	rs10071568	C	A	0.67	0.59	0.36	0.57						Mef2			5 hits	IPO11	intronic
5	62611651	0.87	0.97	rs7729526	G	T	0.70	0.59	0.37	0.57						19 altered motifs			7 hits	IPO11	intronic
5	62620506	0.86	0.95	rs6449601	G	A	0.65	0.59	0.36	0.56						Pax-5			6 hits	IPO11	intronic
5	62624214	0.9	0.99	rs6888641	A	G	0.68	0.59	0.37	0.57			ESDR			Mef2			6 hits	IPO11	intronic
5	62630552	1	1	rs918606	G	A	0.58	0.57	0.36	0.55						CHOP::CEBPalpha,Zbtb3			6 hits	2kb 3' of IPO11	
5	62630910	0.91	1	rs10072795	T	C	0.58	0.58	0.37	0.57						Ik-2,Ik-3,Pou2f2			10 hits	2.3kb 3' of IPO11	
5	62635736	0.9	1	rs1541677	C	A	0.64	0.58	0.37	0.57						4 altered motifs			8 hits	7.2kb 3' of IPO11	
5	62637242	0.89	0.99	rs6449602	A	G	0.38	0.56	0.37	0.57			STRM			Hoxb3			7 hits	8.7kb 3' of IPO11	

Query SNP: rs75834976 and variants with r^2 >= 0.8

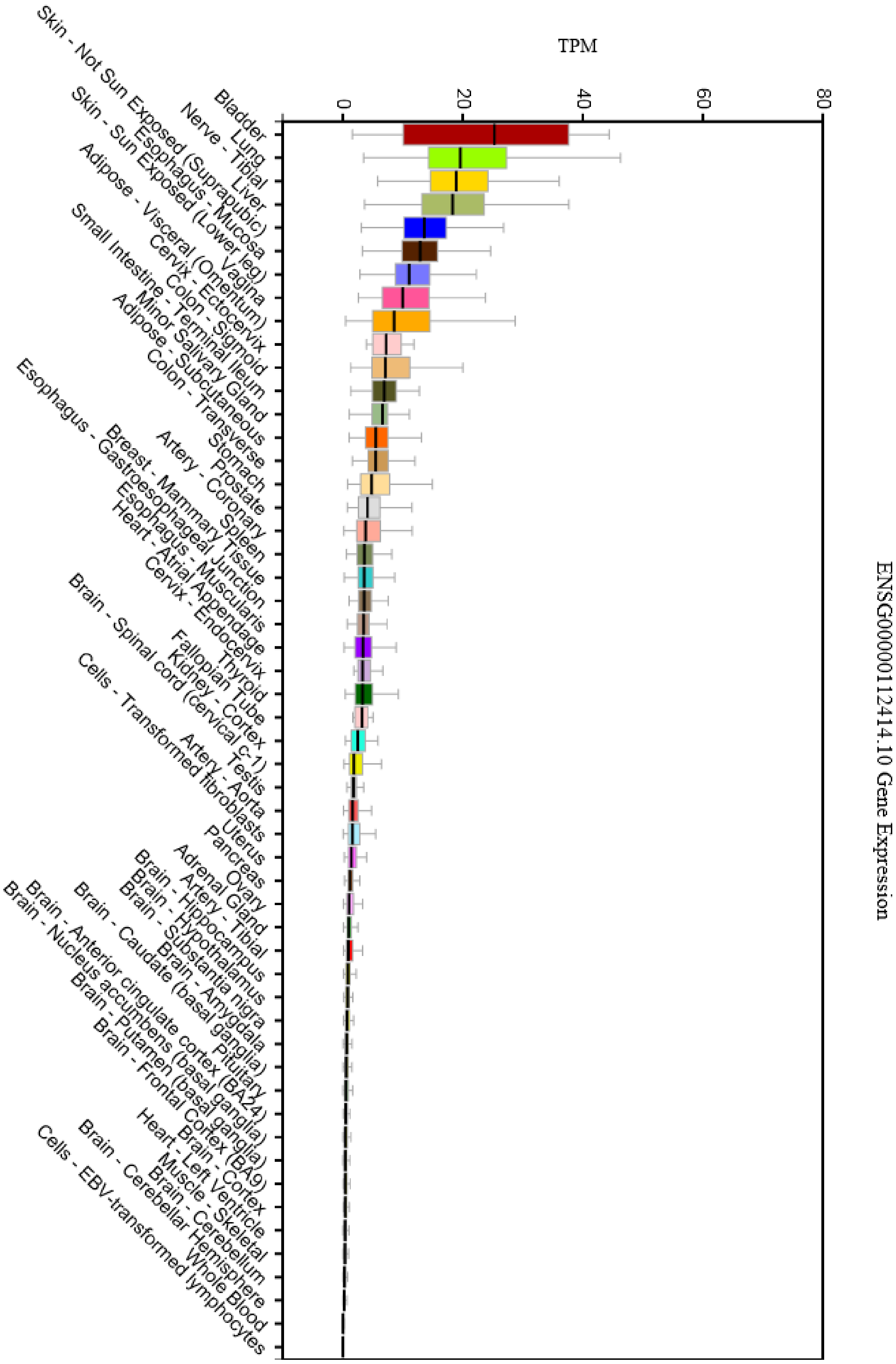
chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
4	5219085	0.91	1	rs16836905	C	G	0.18	0.10	0.07	0.05			ESC, IPSC			5 altered motifs				STK32B	intronic
4	5227791	1	1	rs77224873	G	A	0.05	0.09	0.08	0.04						9 altered motifs				STK32B	intronic
4	5229559	1	1	rs76308788	C	T	0.02	0.09	0.08	0.04										STK32B	intronic
4	5229983	1	1	rs75834976	C	A	0.10	0.10	0.08	0.04						Cart1,Evi-1,TATA				STK32B	intronic

Query SNP: rs56315120 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
1	165199632	1	1	rs56315120	G	A	0.00	0.04	0.00	0.05						8 altered motifs				2.2kb 3' of LMX1A	

Figure E4 GTEx output of *ADGRG6* expression in different tissues
GTEx portal, http://www.gtexportal.org/home/

Date of data extraction:18-September-2017



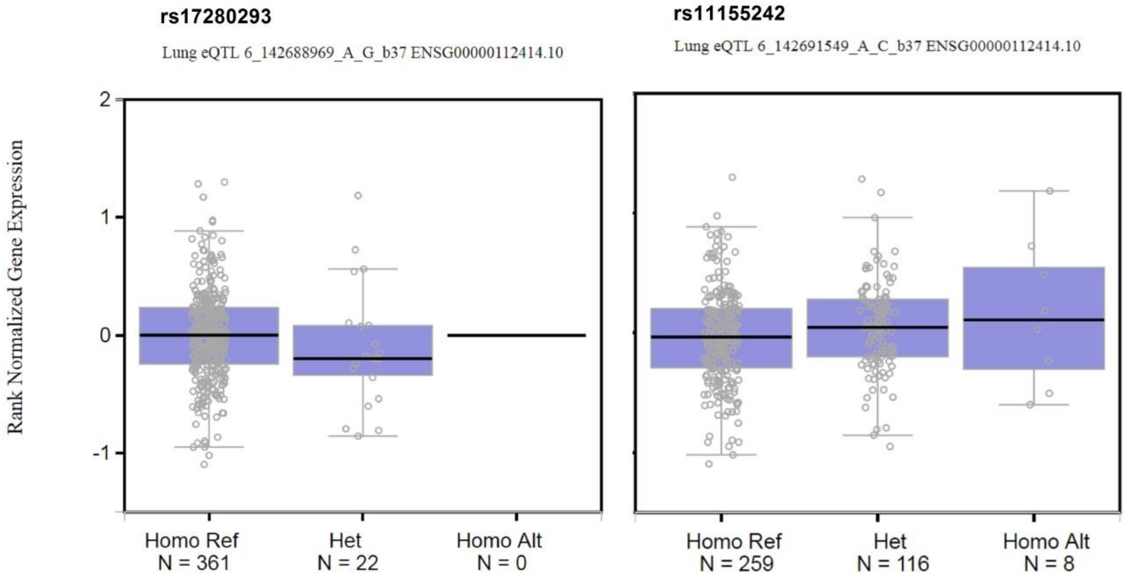


Figure E5 The genotypes of rs17280293 and rs11155242 in GTEx lung tissue database.

This figure is extracted from the GTEx portal. The legend on the top of the figure includes information on: tissue, analysis, chromosome_position_reference allele_effect allele_build and gene ID (*GPR126*). Important note, the effect alleles in this analysis are the reference alleles in the GWAS; therefor, for any comparison with the GWAS results, the effect estimates of the eQTL analysis must be flipped.

Supplemental references

1. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26(4):720-35.
2. Yang J, Lee SH, Wray NR, Goddard ME, Visscher PM. GCTA-GREML accounts for linkage disequilibrium when estimating genetic variance from genome-wide SNPs. Proc Natl Acad Sci U S A. 2016;113(32):E4579-80.
3. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. American Journal of Human Genetics. 1998;62(5):1198-211.
4. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics C, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015;47(3):291-5.
5. Wain LV, Shrine N, Artigas MS, Erzurumluoglu AM, Noyvert B, Bossini-Castillo L, et al. Genome-wide association analyses for lung function and chronic obstructive pulmonary disease identify new loci and potential druggable targets. Nat Genet. 2017;49(3):416-25.
6. Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, et al. Defining the role of common variation in the genomic and biological architecture of adult human height. Nat Genet. 2014;46(11):1173-86.
7. Hobbs BD, de Jong K, Lamontagne M, Bosse Y, Shrine N, Artigas MS, et al. Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis. Nat Genet. 2017;49(3):426-32.
8. Cho MH, Castaldi PJ, Hersh CP, Hobbs BD, Barr RG, Tal-Singer R, et al. A Genome-Wide Association Study of Emphysema and Airway Quantitative Imaging Phenotypes. Am J Respir Crit Care Med. 2015;192(5):559-69.
9. Benner C, Spencer CC, Havulinna AS, Salomaa V, Ripatti S, Pirinen M. FINEMAP: efficient variable selection using summary data from genome-wide association studies. Bioinformatics. 2016;32(10):1493-501.
10. Pasaniuc B, Price AL. Dissecting the genetics of complex traits using summary association statistics. Nat Rev Genet. 2017;18(2):117-27.
11. Vandesompele J, De Preter K, Pattyn F, Poppe B, Van Roy N, De Paepe A, et al. Accurate normalization of real-time quantitative RT-PCR data by geometric averaging of multiple internal control genes. Genome Biol. 2002;3(7):RESEARCH0034.
12. Crapo RO, Jensen RL, Wanger JS. Single-breath carbon monoxide diffusing capacity. Clin Chest Med. 2001;22(4):637-49.
13. Loth DW, Soler Artigas M, Gharib SA, Wain LV, Franceschini N, Koch B, et al. Genome-wide association analysis identifies six new loci associated with forced vital capacity. Nat Genet. 2014;46(7):669-77.