

## **Supplementary Figures:**

### **Supplementary Figure 1** Study design for X chromosome analyses

#### **STAGE 1 (genome-wide association studies)**

**n=33009**

B58C (n=5934)  
BHS1&2 (n=4355)  
CROATIA-Korcula (n=826)  
CROATIA-Split (n=493)  
CROATIA-Vis (n=925)  
GS:SFHS (n=8086)  
H2000 (n=748)  
KORA F4 (n=1378)  
KORA S3 (n=1147)  
LBC1936 (n=991)  
NFBC1966 (n=4563)  
SAPALDIA (n=1378)  
SHIP (n=1766)  
YFS (n=419)



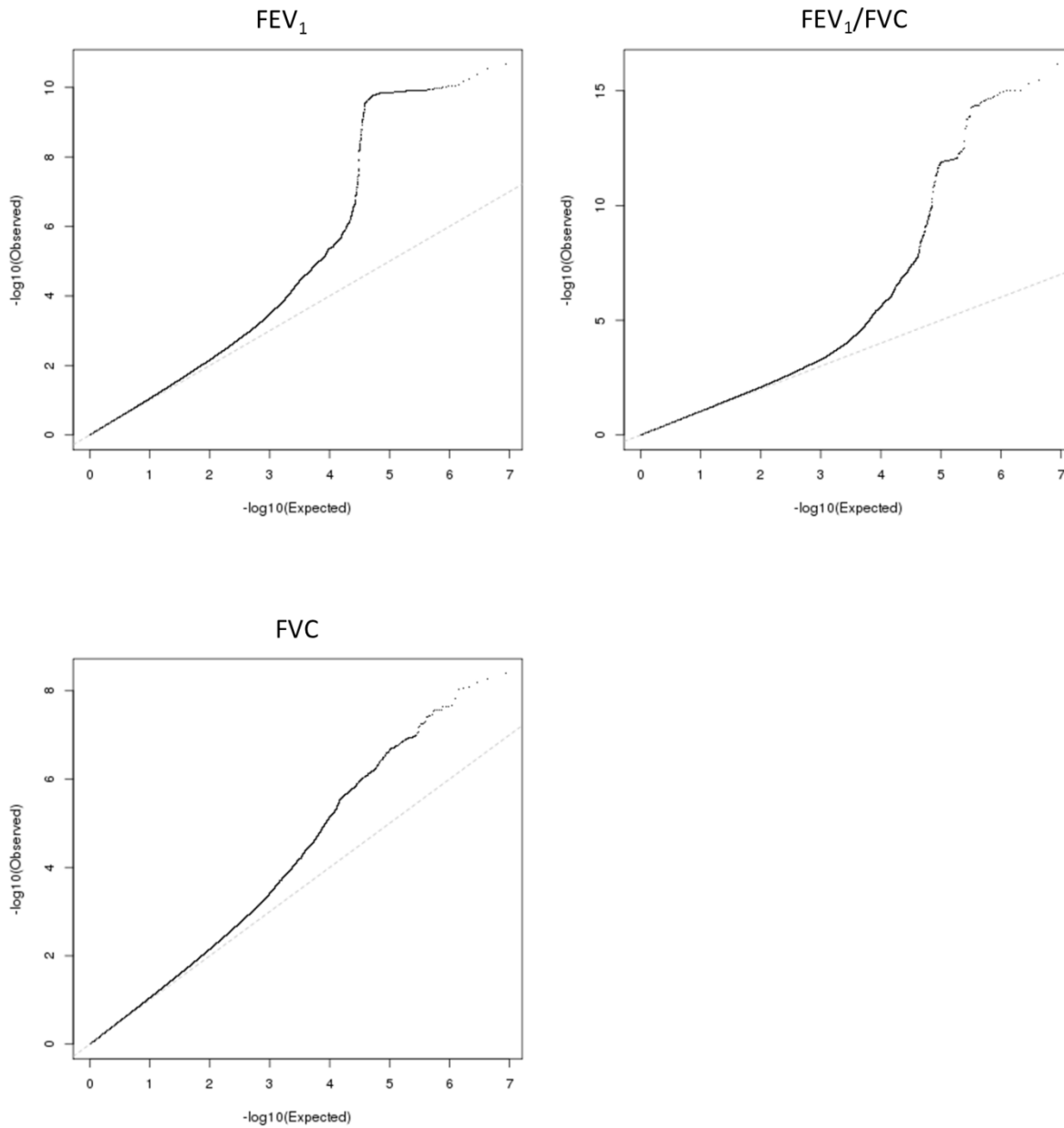
#### **STAGE 2 (follow up studies)**

**n=52359**

PIVUS (n=837)  
TwinsUK (n=2579)  
UK BiLEVE (n=48943)

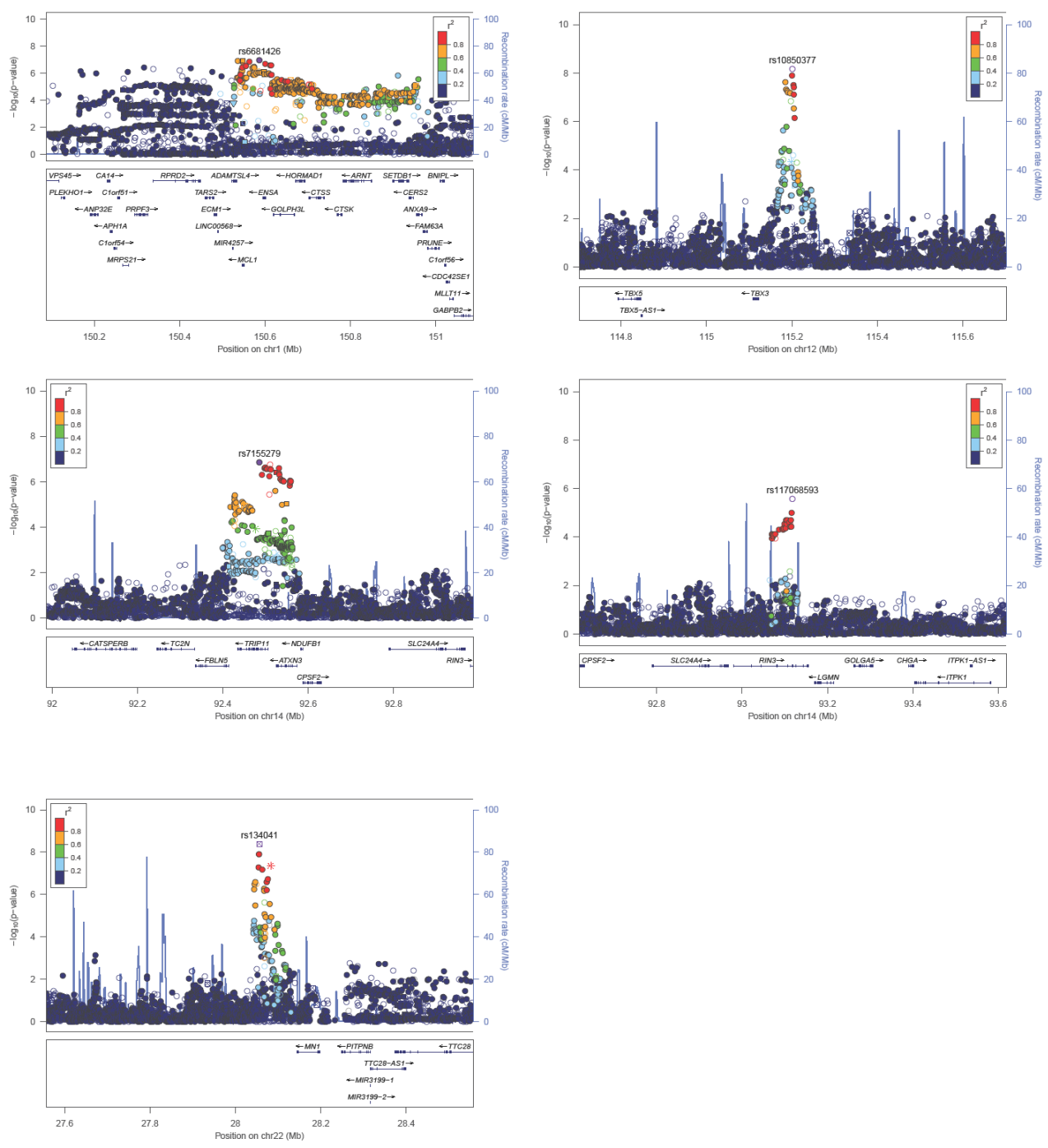
The discovery stage (stage 1) included 14 studies and 33,009 individuals. One variant was followed up in stage 2 in 3 studies and 52,359 individuals.

## Supplementary Figure 2 Association test statistics for FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and FVC

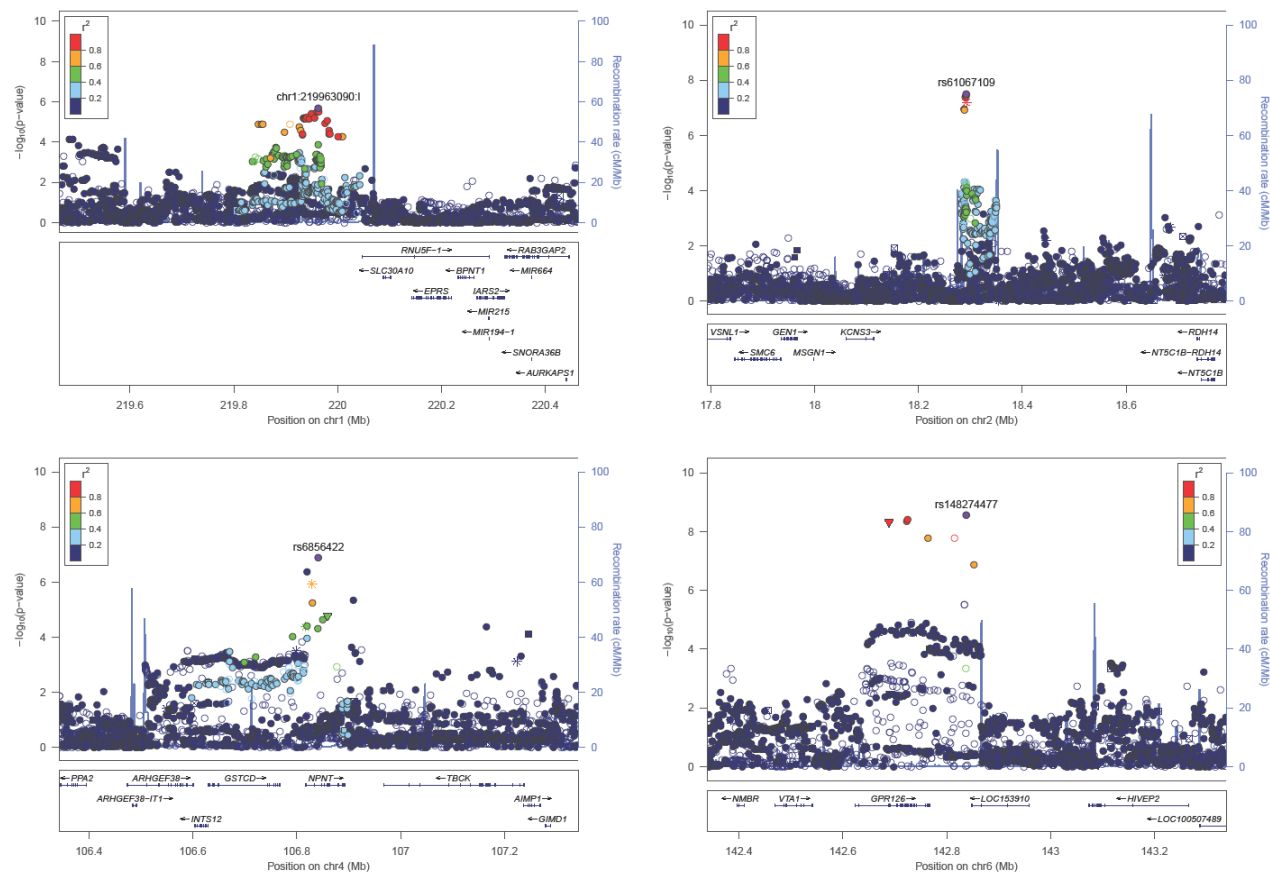


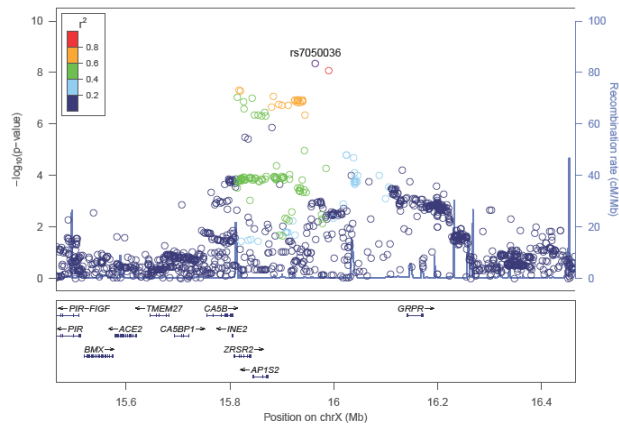
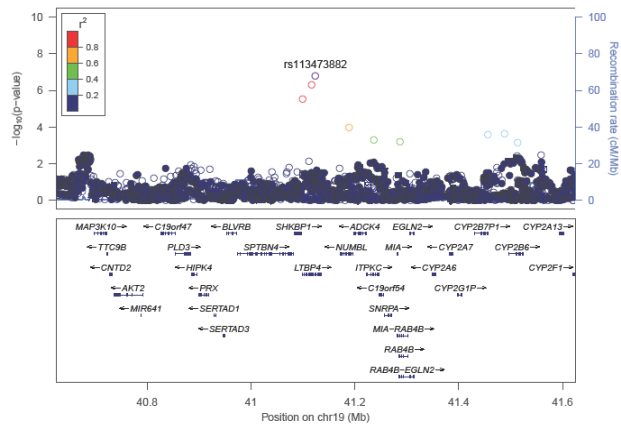
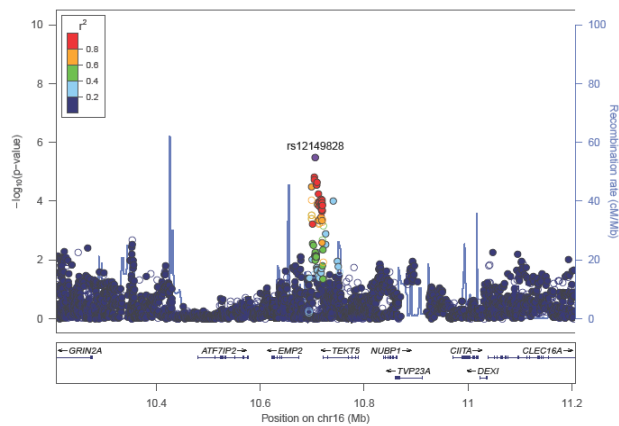
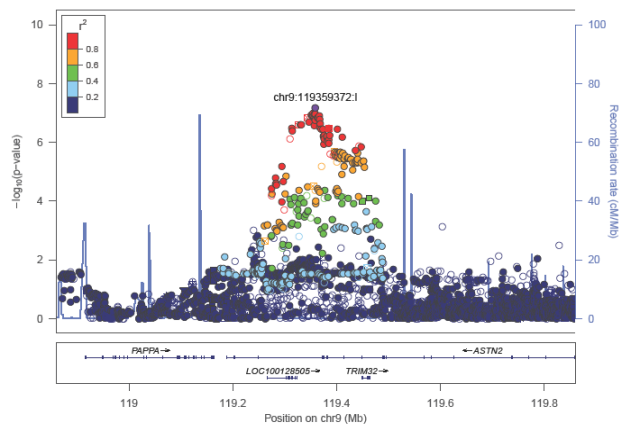
- a) Quantile-quantile plots. QQplots show  $-\log_{10}(P)$  of observed genome-wide association results against expected results in case of no association for autosomal chromosomes for FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and FVC. Only variants with effective sample size (product of sample size and imputation quality summed up across studies)  $\geq 70\%$  are included.

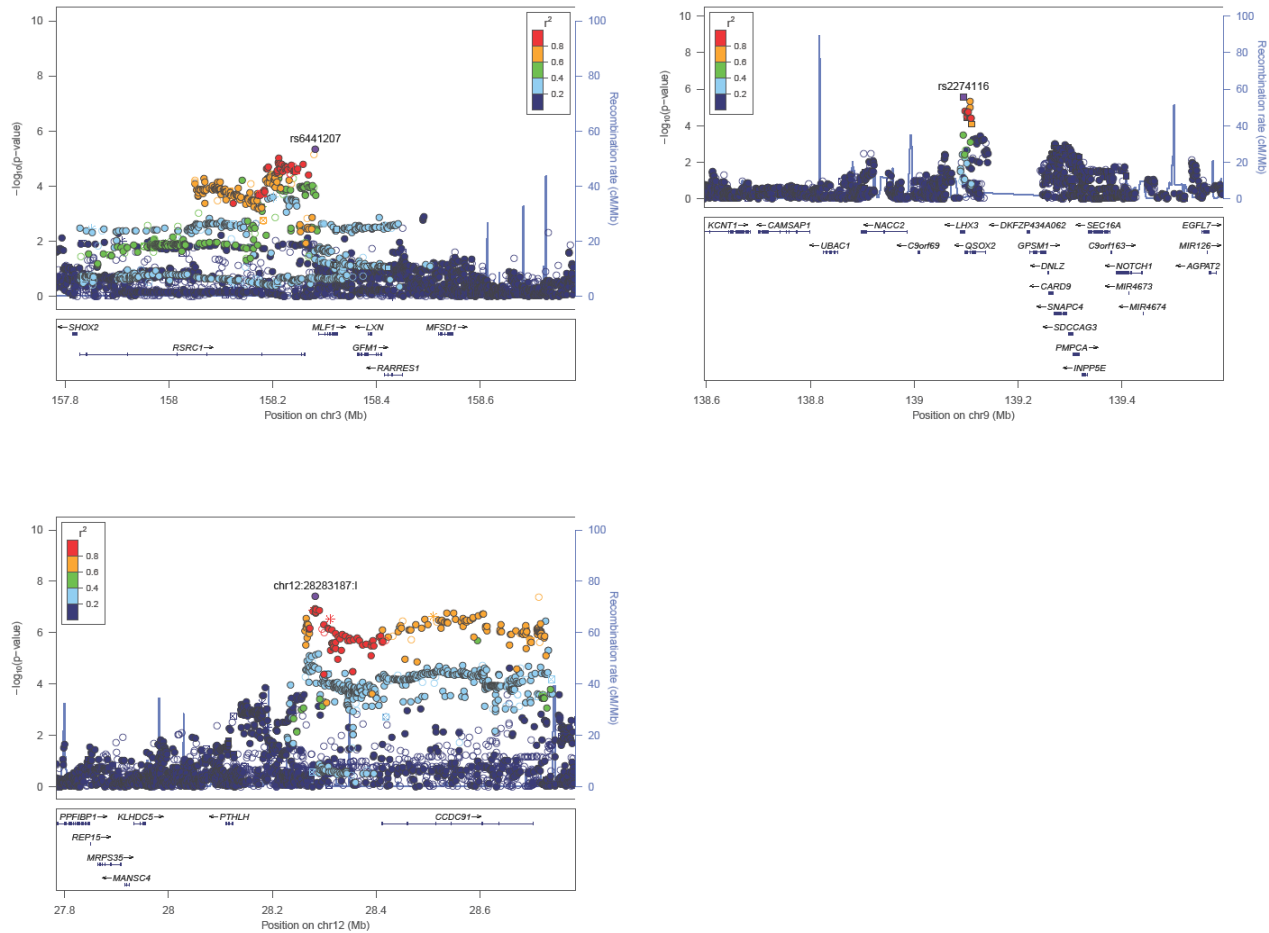
FEV<sub>1</sub>



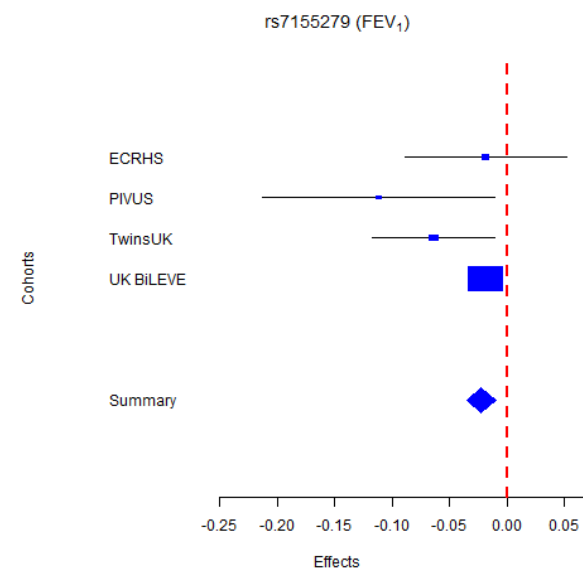
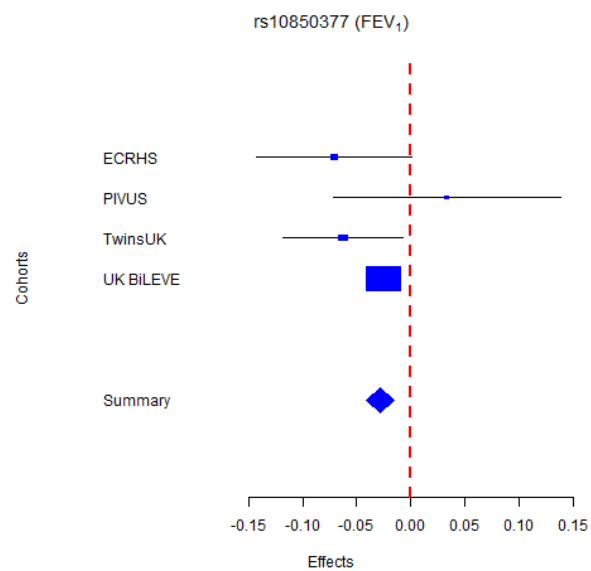
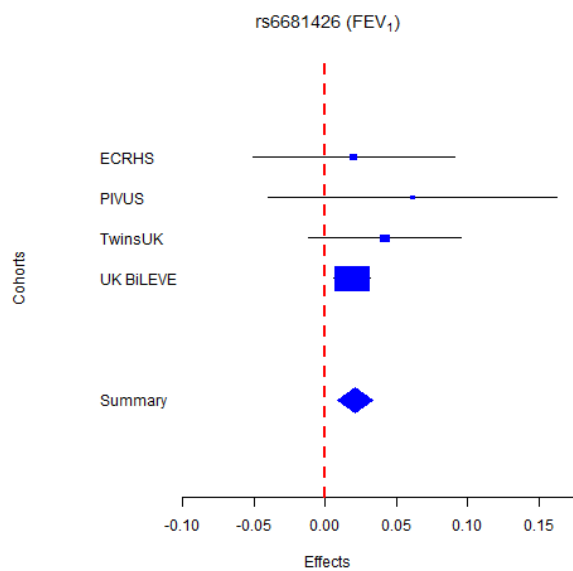
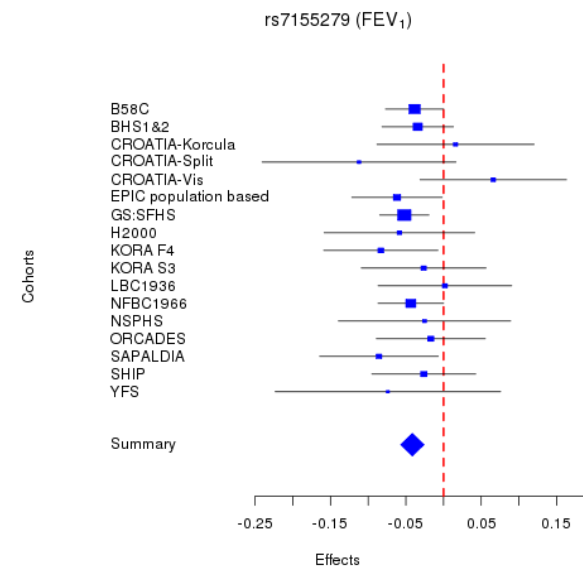
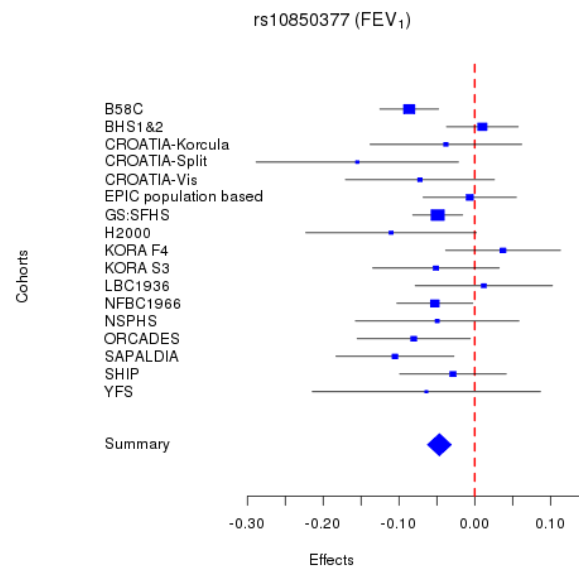
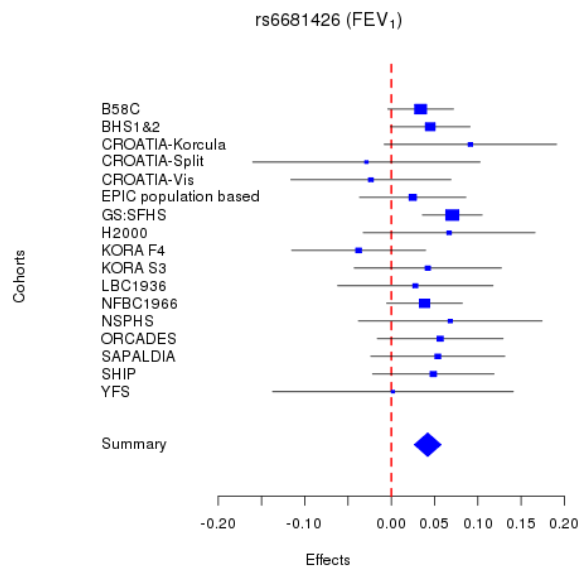
FEV<sub>1</sub>/FVC

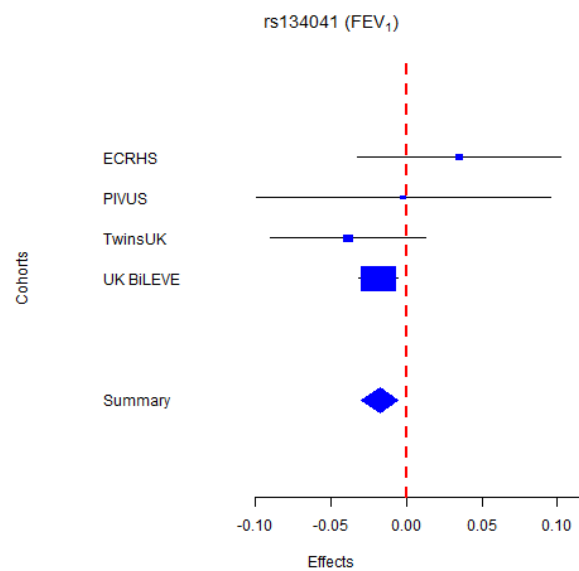
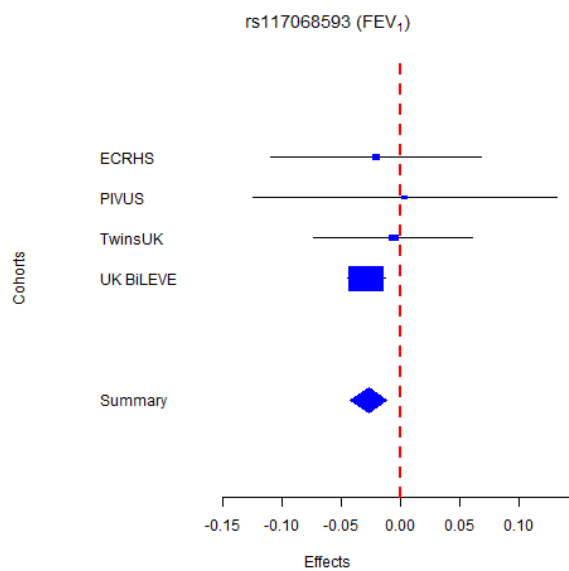
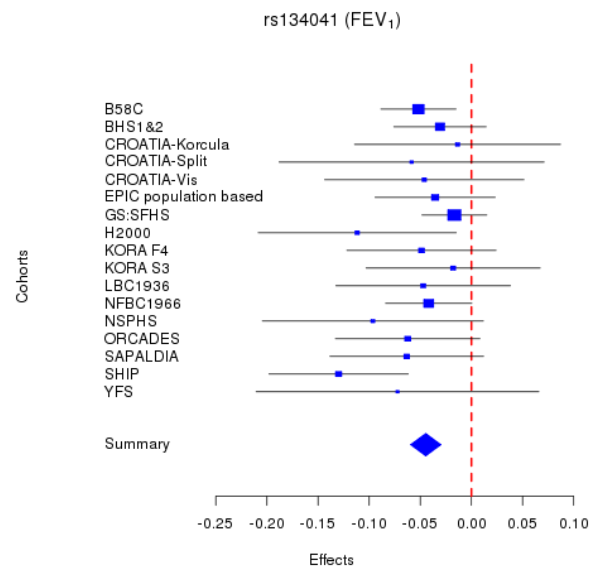
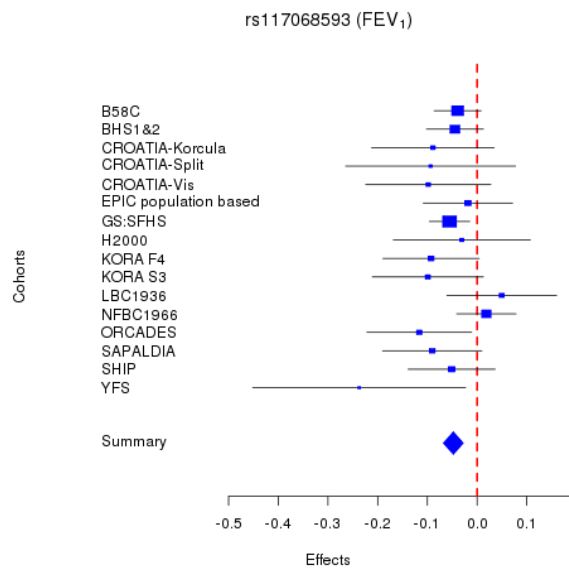


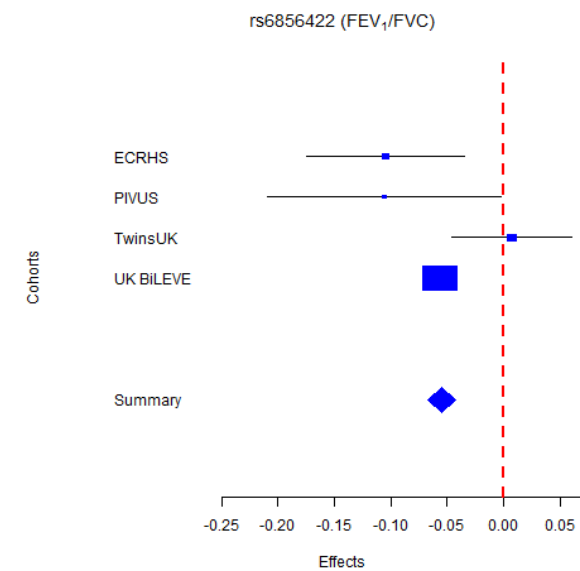
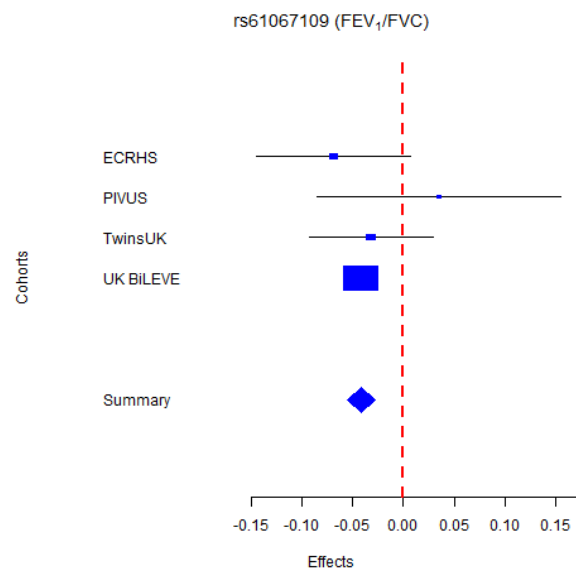
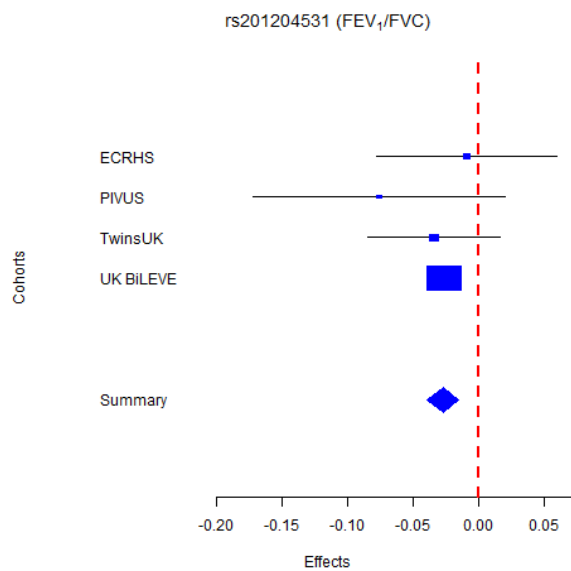
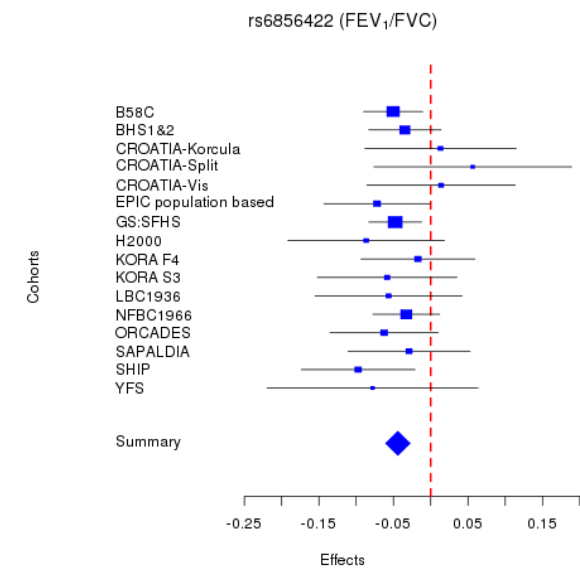
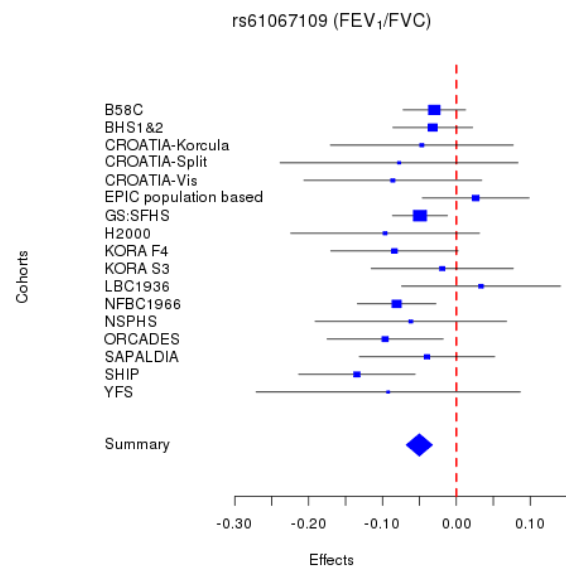
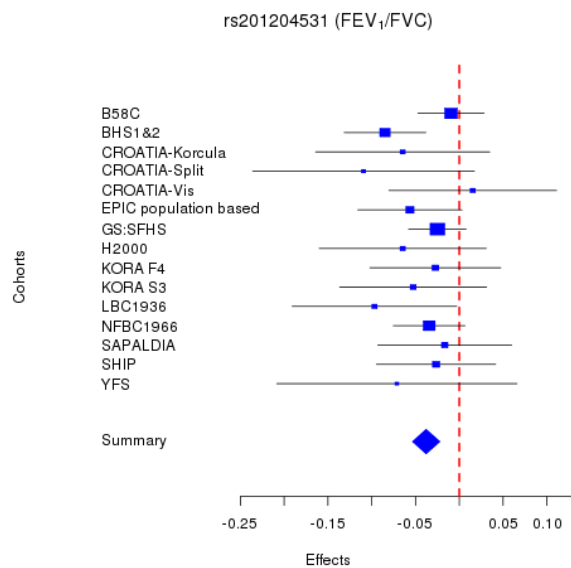


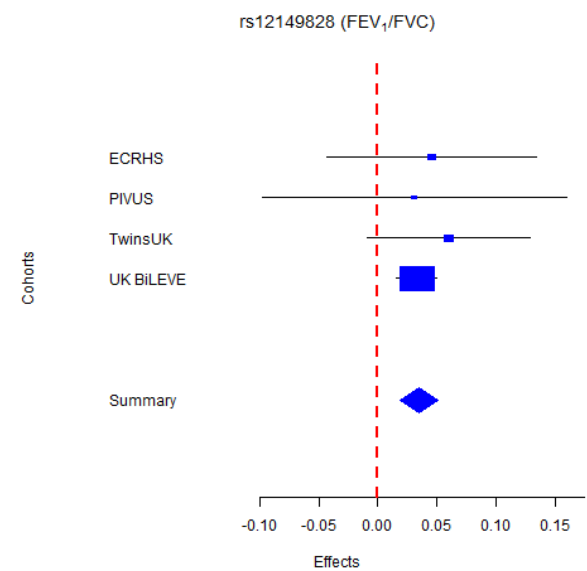
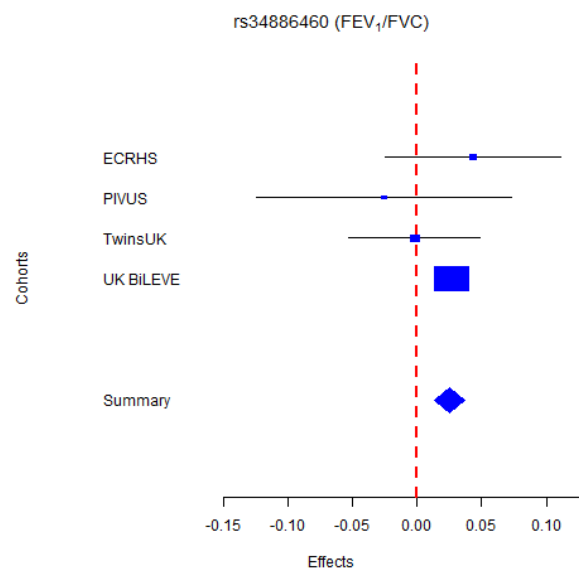
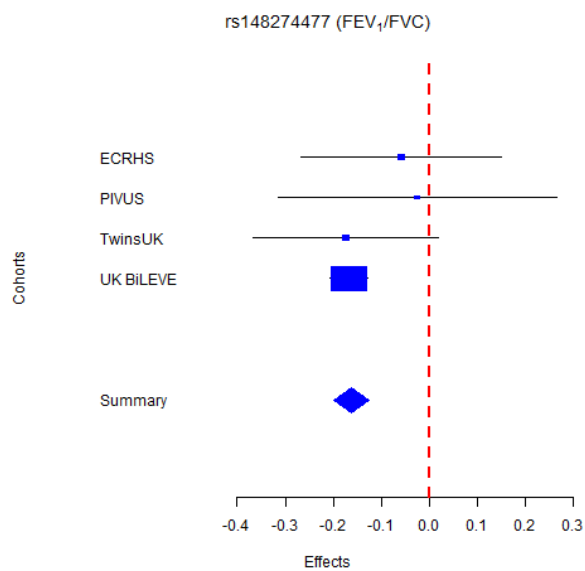
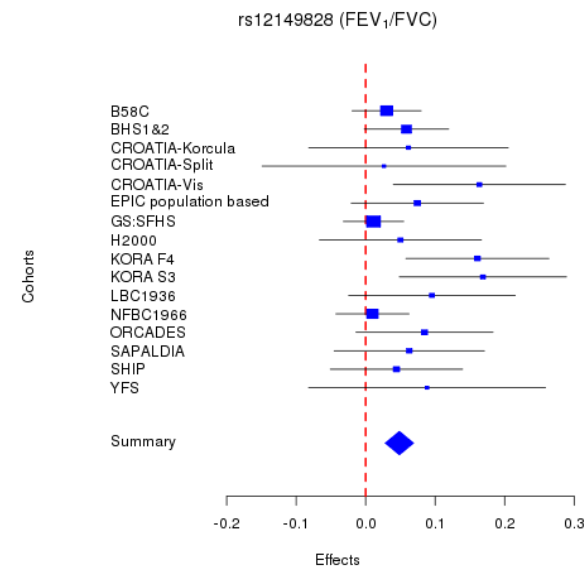
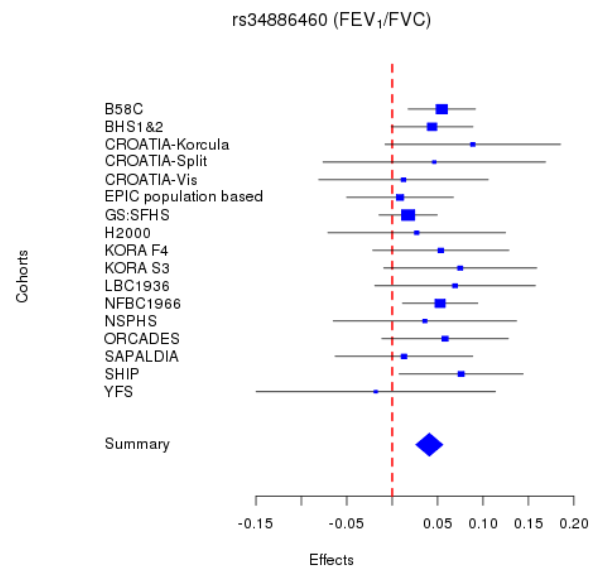
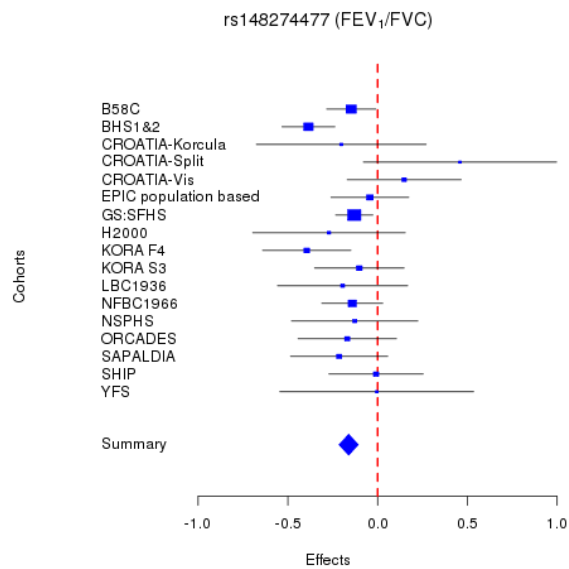


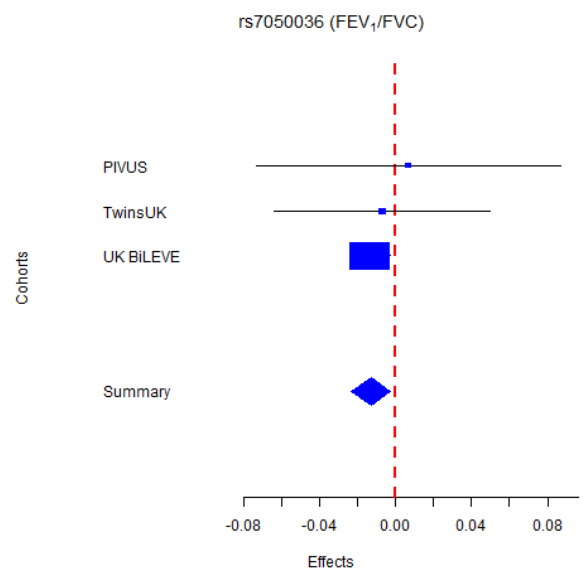
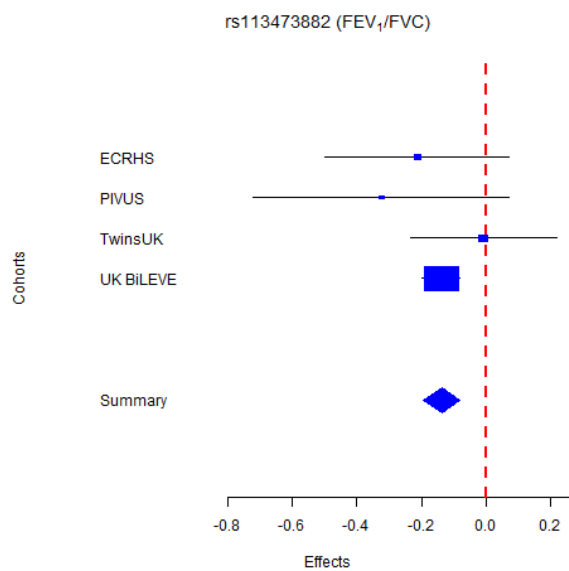
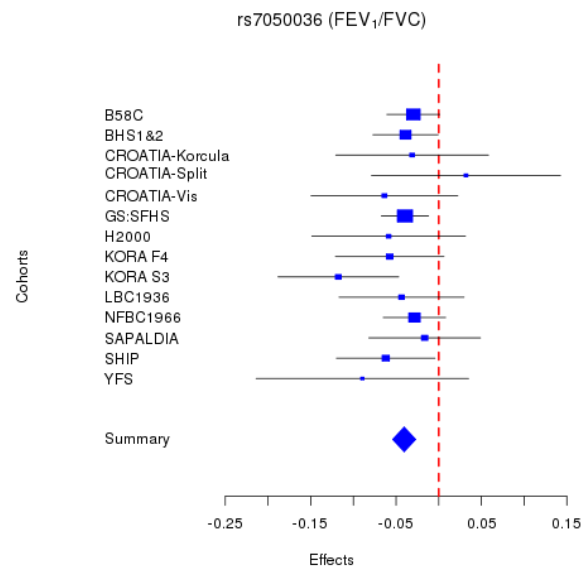
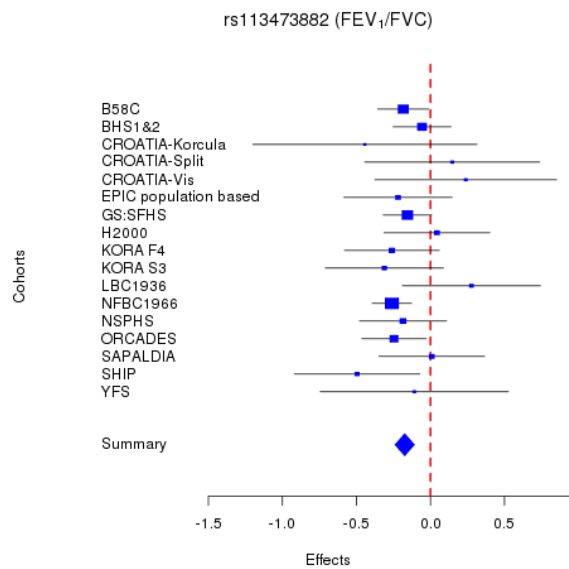
- b) Regional association plots for 16 new lung function signals.  $-\log_{10}(P)$  in stage 1 meta-analysis for the trait with strongest association are plotted against chromosomal position (NCBI 37) for 1Mb regions. Sentinel variants in each plot and represented in purple. Other variants are coloured according to their correlation with the sentinel variant (see legend in each plot). Annotation for each variant is presented as default in locuszoom (<http://csg.sph.umich.edu/locuszoom/>): framestop and splice, triangle; non synonymous, inverted triangle; synonymous and UTR, square; TFBScons, star; MCS44 Placental, square with diagonal lines and None-of-the-above, filled circle.

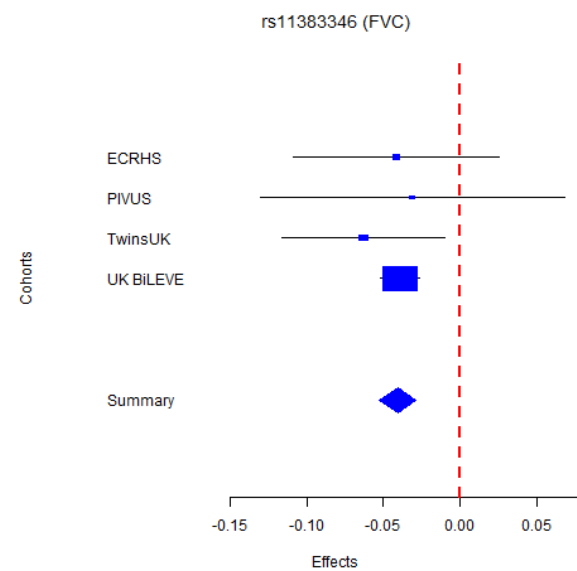
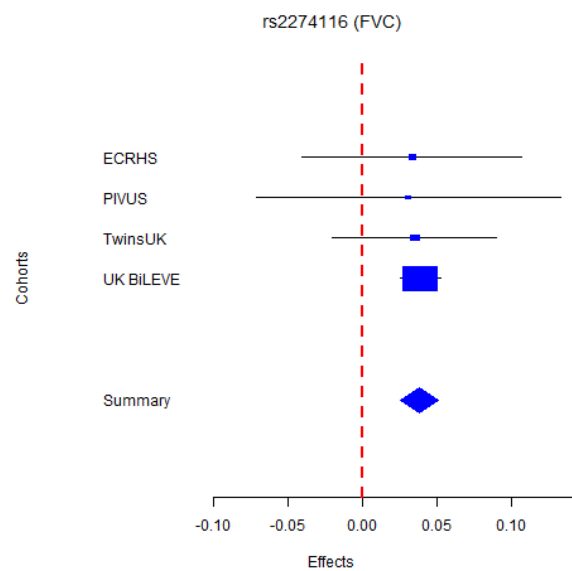
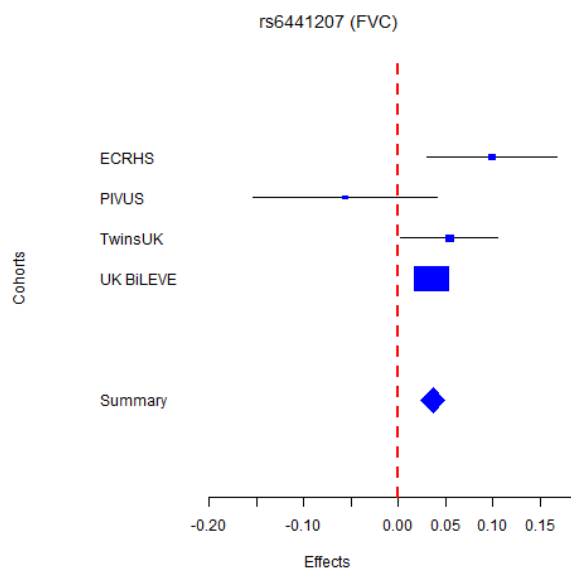
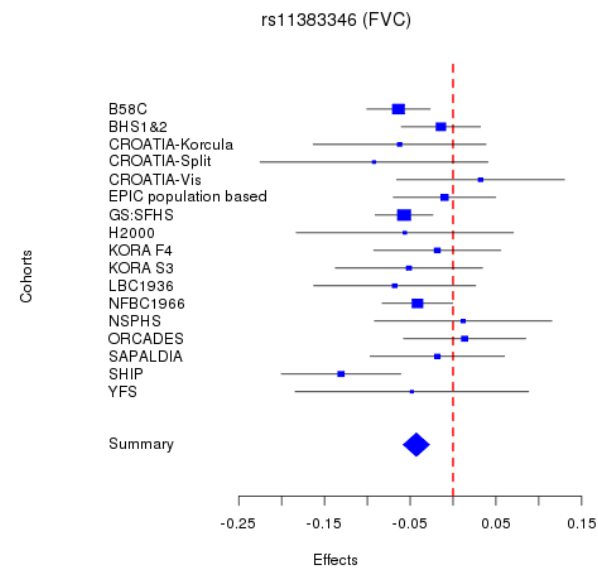
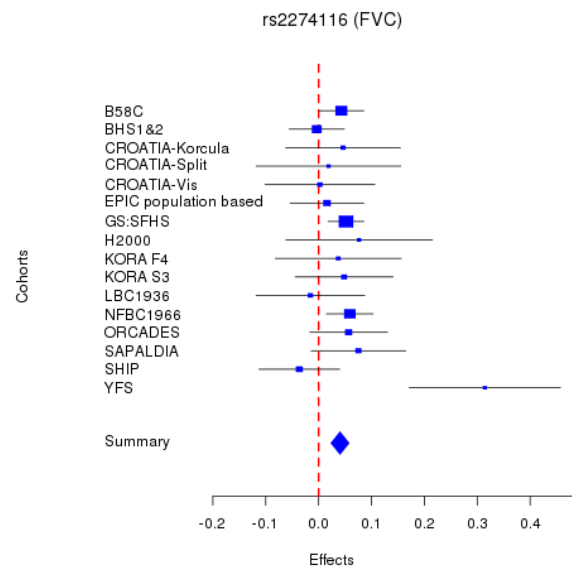
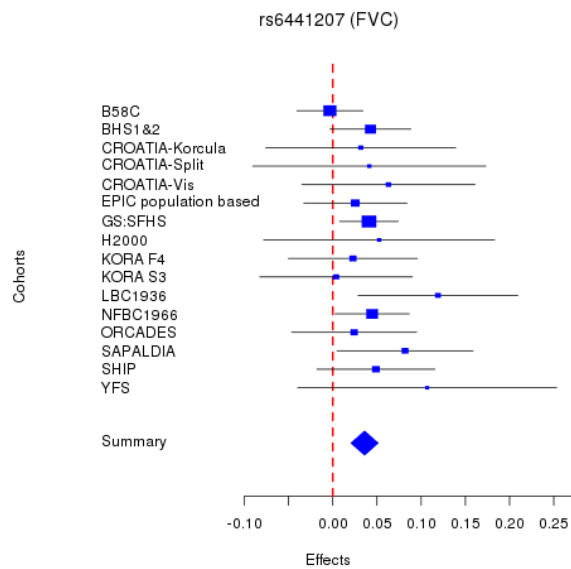








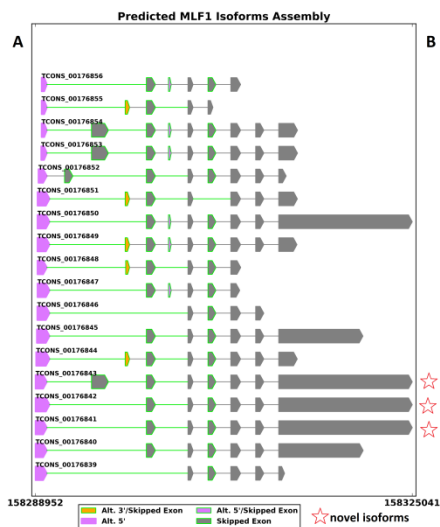




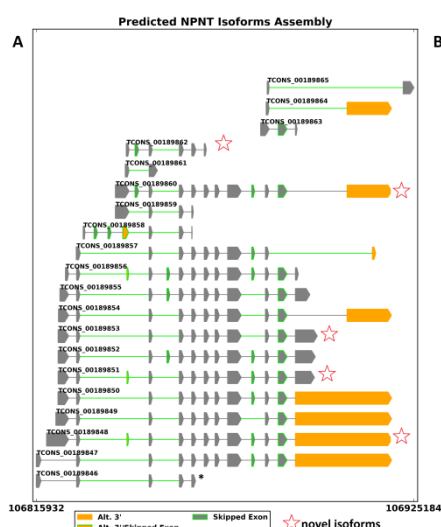
- c) Forest plots for the 16 loci associated with lung function for stage 1 and stage 2 separately. Each of the SNPs included in the figure showed genome-wide significant association ( $P < 5 \times 10^{-8}$ ) with either FEV<sub>1</sub>, FEV<sub>1</sub>/FVC or FVC after meta-analysing stages 1 and 2. The contributing effect (transformed beta) from each study is shown by a square, with confidence intervals indicated by horizontal lines. The contributing weight of each study to the meta-analysis is indicated by the size of the square. The combined meta-analysis estimate is shown at the bottom of each graph.

Supplementary Figure 3 Transcriptomic profiling of candidate lung function genes in primary human bronchial epithelial cells.

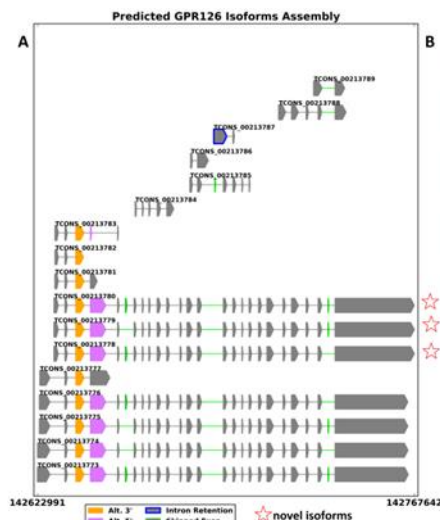




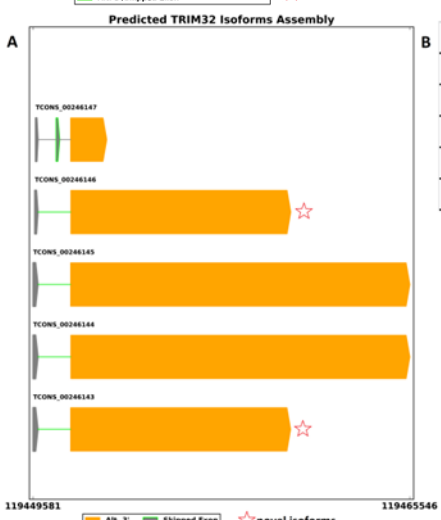
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| TCONS_00176850 | Less than 1%          |
| TCONS_00176849 | Less than 1%          |
| TCONS_00176848 | Between 1 and 5%      |
| TCONS_00176847 | Between 10 and 20%    |
| TCONS_00176846 | Between 1 and 5%      |
| TCONS_00176845 | Between 5 and 10%     |
| TCONS_00176844 | Between 30 and 40%    |
| TCONS_00176843 | Less than 1%          |
| TCONS_00176842 | Less than 1%          |
| TCONS_00176841 | Less than 1%          |
| TCONS_00176840 | Between 30 and 40%    |
| TCONS_00176839 | Between 5 and 10%     |



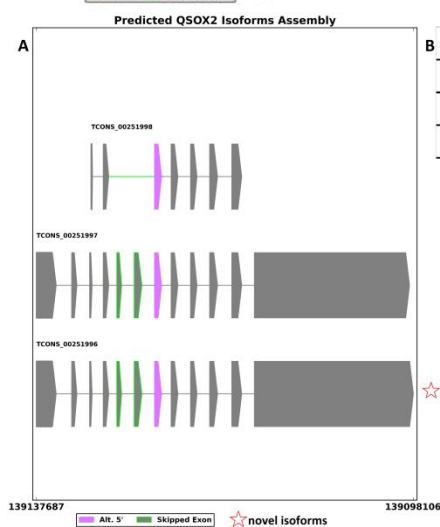
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| TCONS_00189858 | Between 1 and 5%      |
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| TCONS_00189854 | Less than 1%          |
| TCONS_00189853 | Less than 1%          |
| TCONS_00189852 | Less than 1%          |
| TCONS_00189851 | Between 1 and 5%      |
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| TCONS_00189849 | Less than 1%          |
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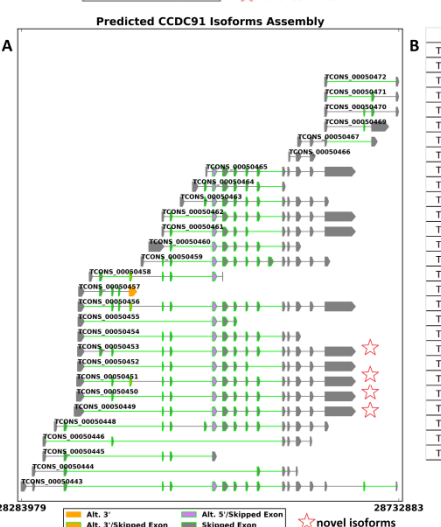
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| TCONS_00213787 | Less than 1%          |
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| TCONS_00213785 | Less than 1%          |
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| TCONS_00213783 | Between 1 and 5%      |
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| TCONS_00213780 | Between 5 and 10%     |
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| TCONS_00213777 | Less than 1%          |
| TCONS_00213776 | Between 10 and 20%    |
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| TCONS_00213774 | Less than 1%          |
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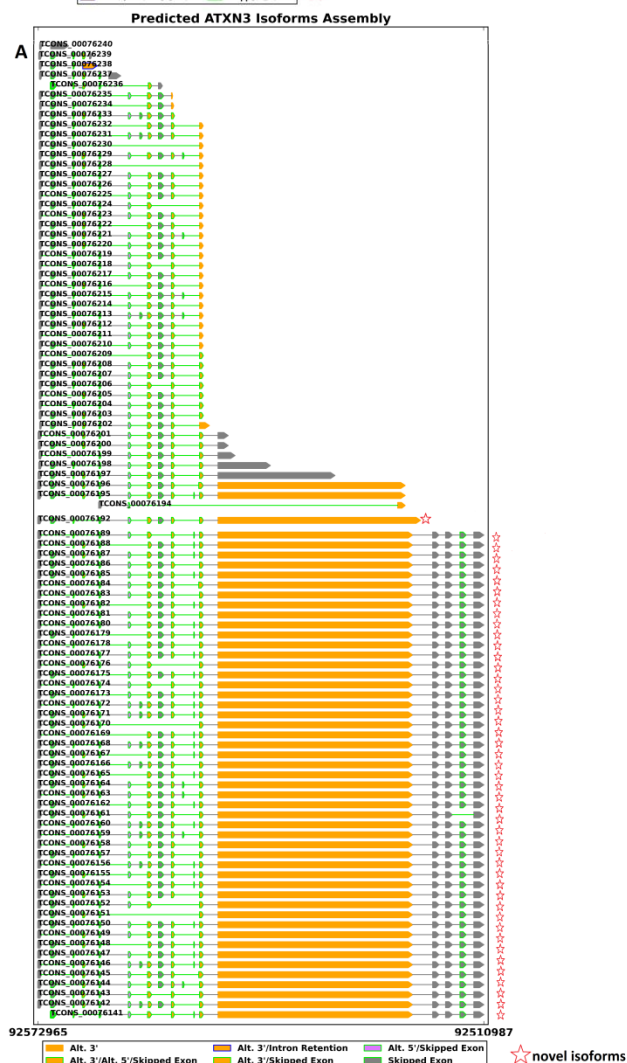
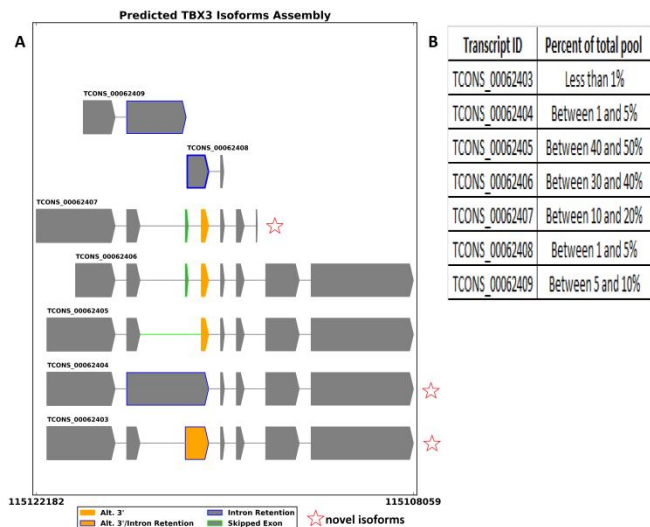
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| TCONS_00246143 | Between 20 and 30%    |

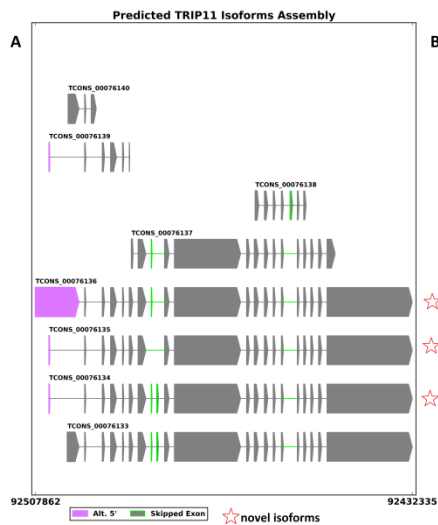


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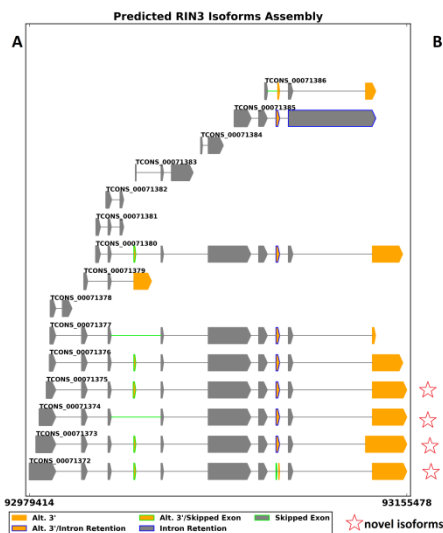
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| TCONS_00050466 | Less than 1%          |
| TCONS_00050465 | Less than 1%          |
| TCONS_00050464 | Between 1 and 5%      |
| TCONS_00050463 | Less than 1%          |
| TCONS_00050462 | Between 30 and 40%    |
| TCONS_00050461 | Less than 1%          |
| TCONS_00050460 | Less than 1%          |
| TCONS_00050459 | Between 1 and 5%      |
| TCONS_00050458 | Less than 1%          |
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| TCONS_00050446 | Less than 1%          |
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| TCONS_00050444 | Less than 1%          |
| TCONS_00050443 | Between 1 and 5%      |





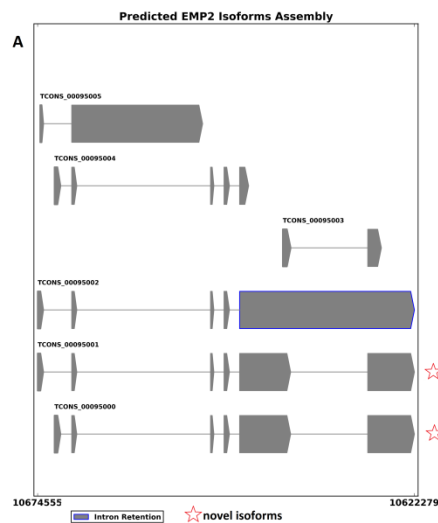
**B**

| Transcript ID  | Percent of total pool |
|----------------|-----------------------|
| TCONS_00076140 | Between 20 and 30%    |
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| TCONS_00076138 | Less than 1%          |
| TCONS_00076137 | Between 50 and 60%    |
| TCONS_00076136 | Less than 1%          |
| TCONS_00076135 | Less than 1%          |
| TCONS_00076134 | Less than 1%          |
| TCONS_00076133 | Between 20 and 30%    |



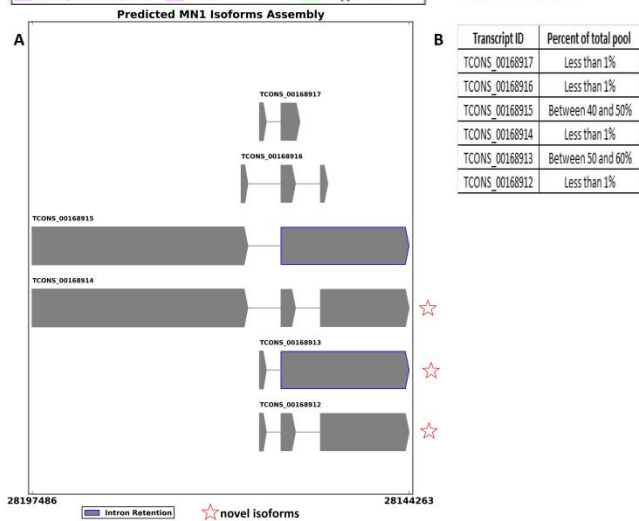
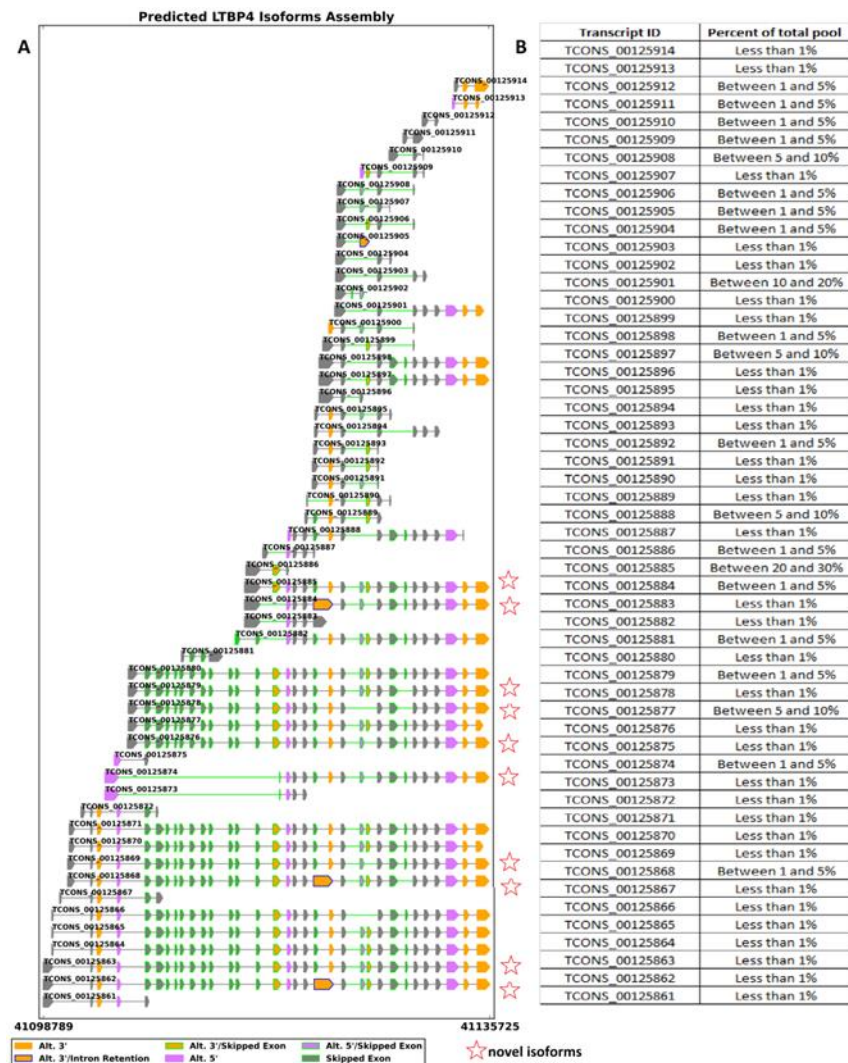
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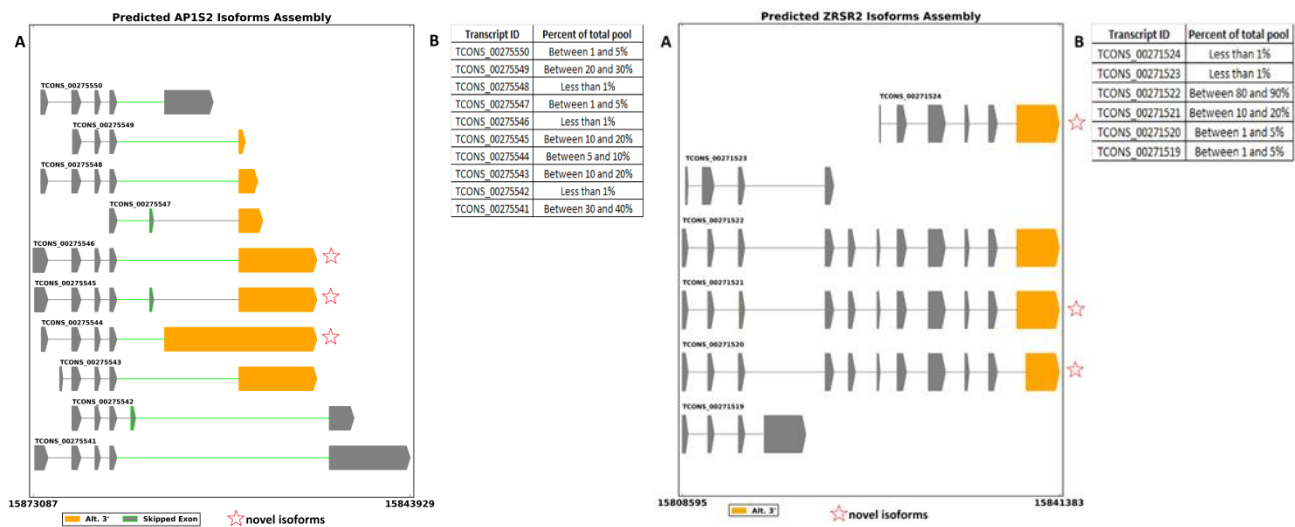
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| TCONS_00071382 | Between 1 and 5%      |
| TCONS_00071381 | Less than 1%          |
| TCONS_00071380 | Less than 1%          |
| TCONS_00071379 | Less than 1%          |
| TCONS_00071378 | Between 1 and 5%      |
| TCONS_00071377 | Between 5 and 10%     |
| TCONS_00071376 | Between 60 and 70%    |
| TCONS_00071375 | Less than 1%          |
| TCONS_00071374 | Between 5 and 10%     |
| TCONS_00071373 | Between 1 and 5%      |
| TCONS_00071372 | Less than 1%          |



**B**

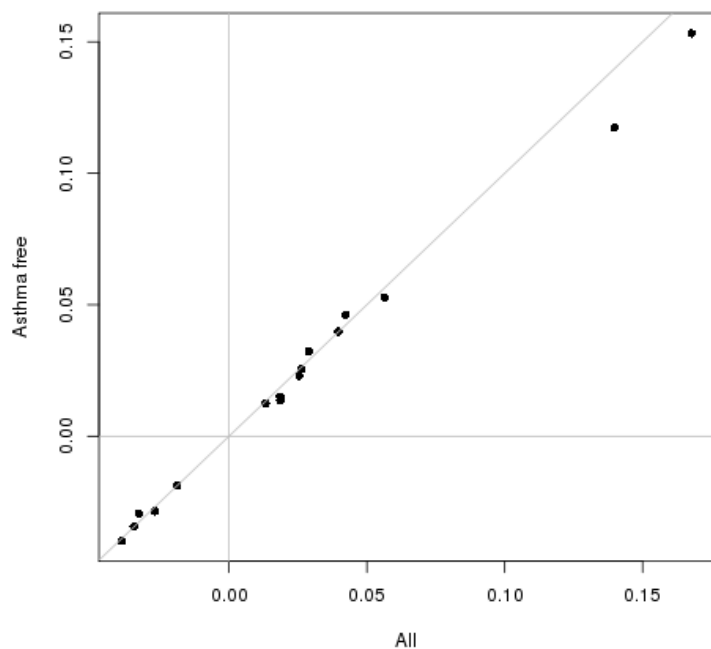
| Transcript ID  | Percent of total pool |
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| TCONS_00095005 | Less than 1%          |
| TCONS_00095004 | Between 20 and 30%    |
| TCONS_00095003 | Less than 1%          |
| TCONS_00095002 | Between 70 and 80%    |
| TCONS_00095001 | Less than 1%          |
| TCONS_00095000 | Less than 1%          |





Figures show novel and previously described (Ensembl) mRNA isoforms and their percent abundance. A: Individual predicted gene's isoforms with indicated splice variation identified using RNA-seq reference annotation based transcript assembly. Different splice events are described in the box beneath the main graph and novel transcripts are indicated by a star. X-axis contains two outmost genomic coordinates. B: Percent abundance of individual transcripts in primary human bronchial epithelial cells (passage 3) grown under basal conditions.

**Supplementary Figure 4** Comparison of results before and after excluding individuals with asthma

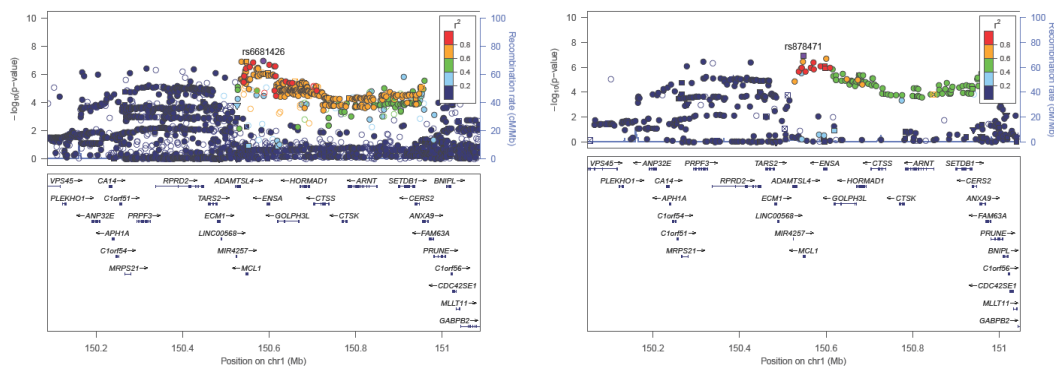


Association results are presented for the 16 novel sentinel variants with the trait that showed the strongest association, for all individuals (“All”, N=48,943) and after removing individuals with asthma (“Asthma free”, N=41,455) using UK BiLEVE data.

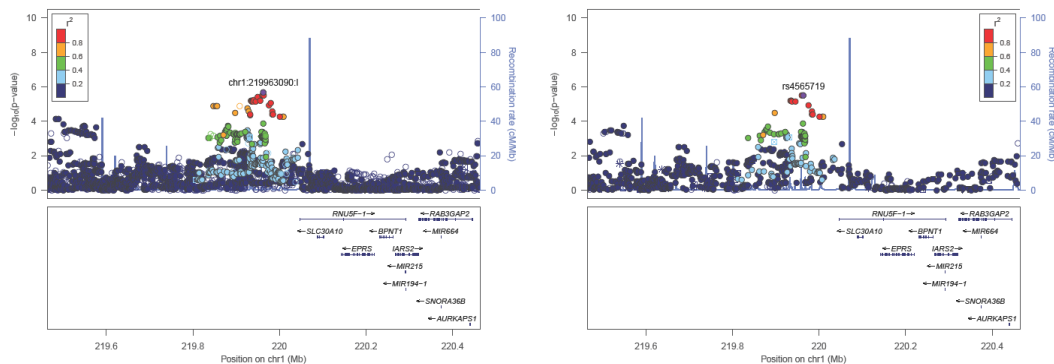
# Supplementary Figure 5 Comparison of results obtained with 1000 Genomes variants and with HapMap for autosomal signals

## a) Region plots for the new signals using HapMap and 1000 Genomes variants

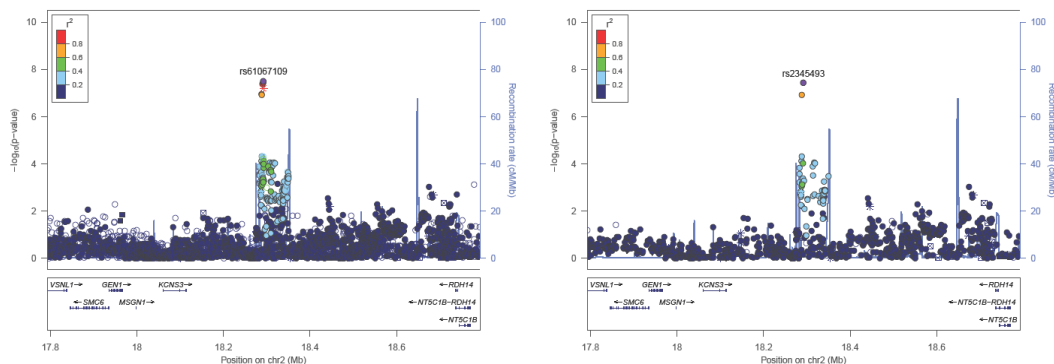
### i. rs6681426



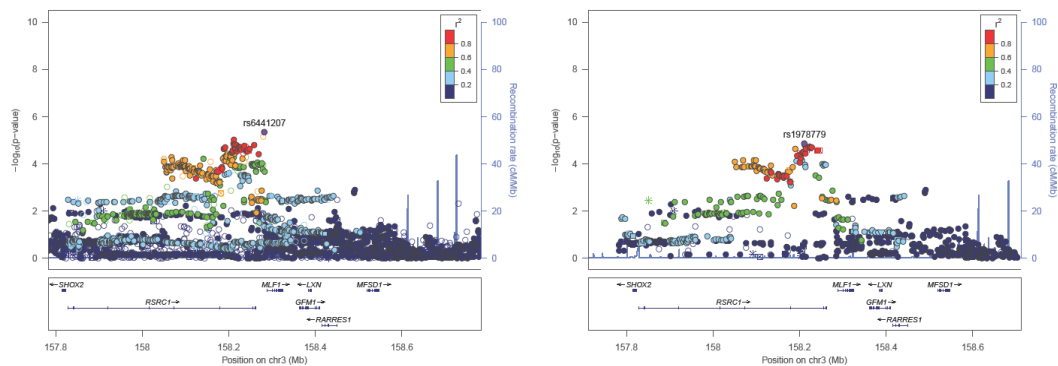
### ii. rs201204531 (chr1:219963090:I)



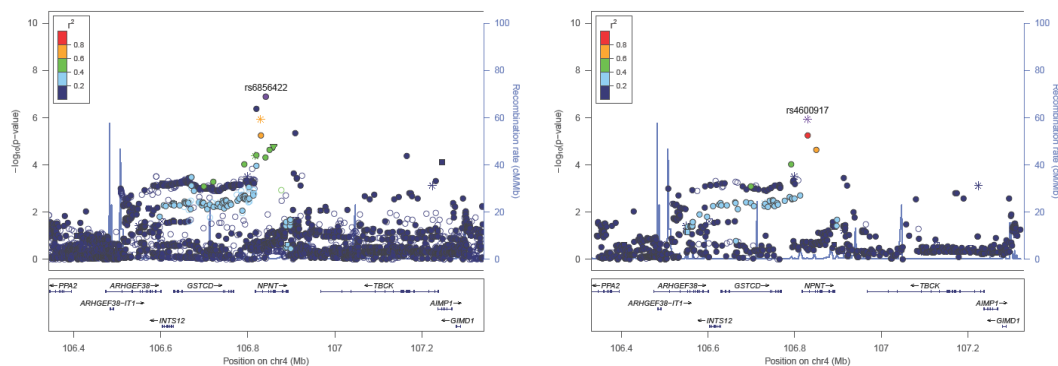
### iii. rs61067109



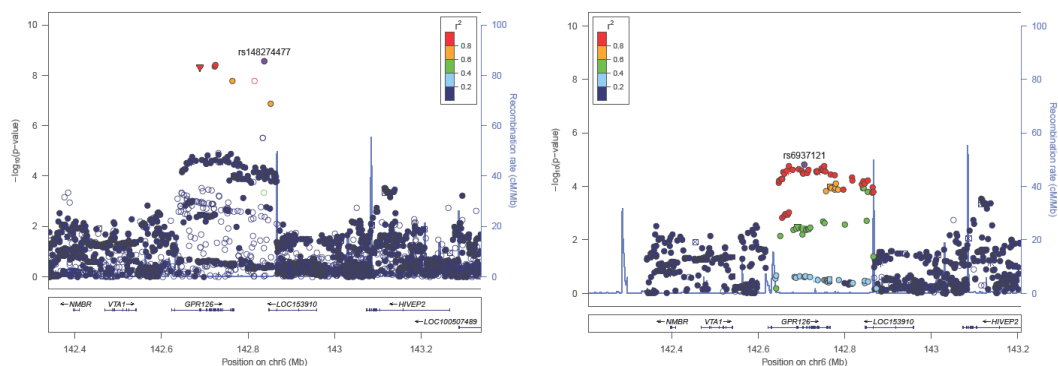
#### iv. rs6441207



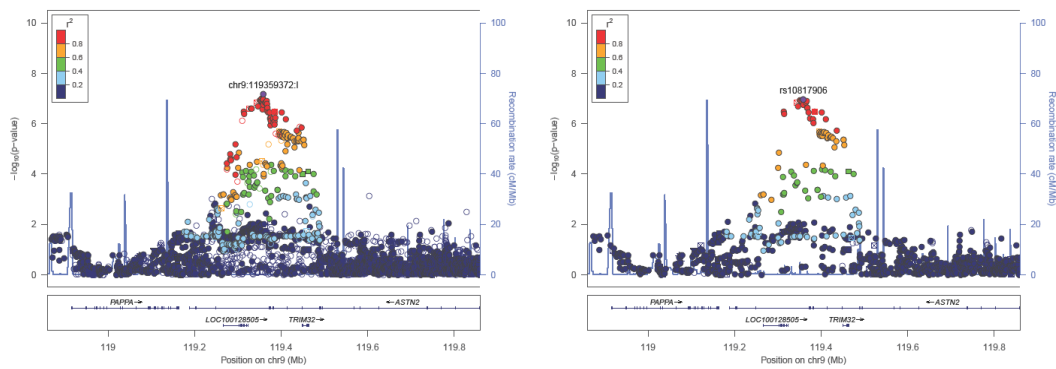
#### v. rs6856422



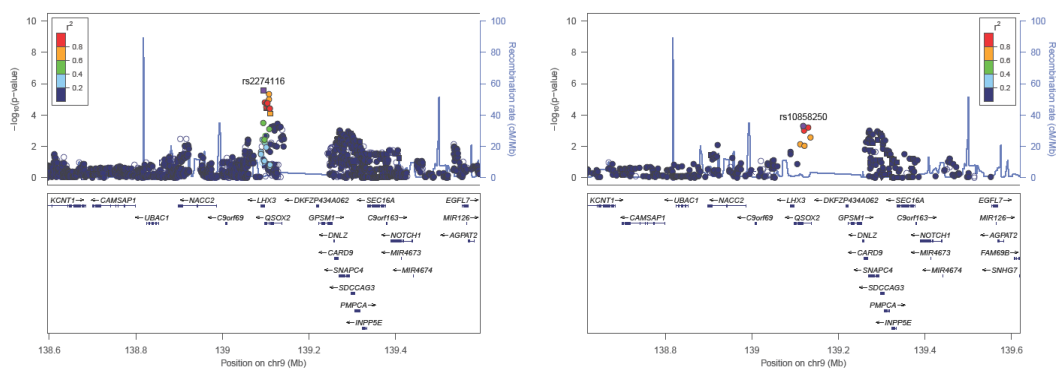
#### vi. rs148274477



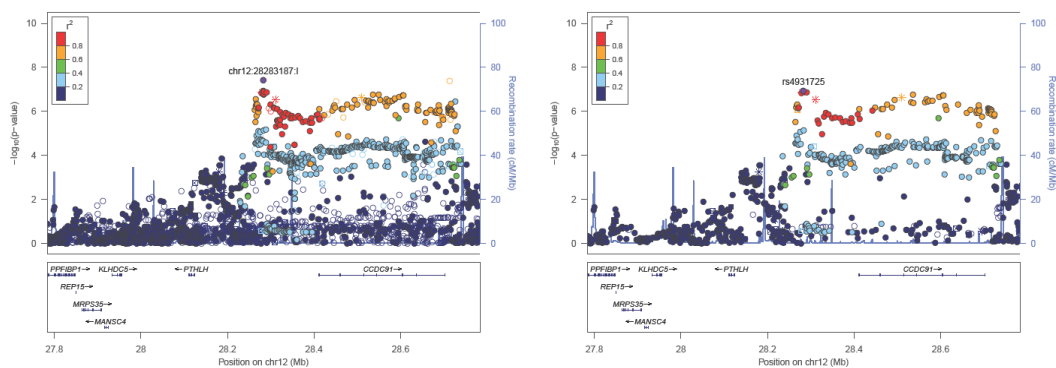
vii. rs34886460 (chr9:119359372:l)



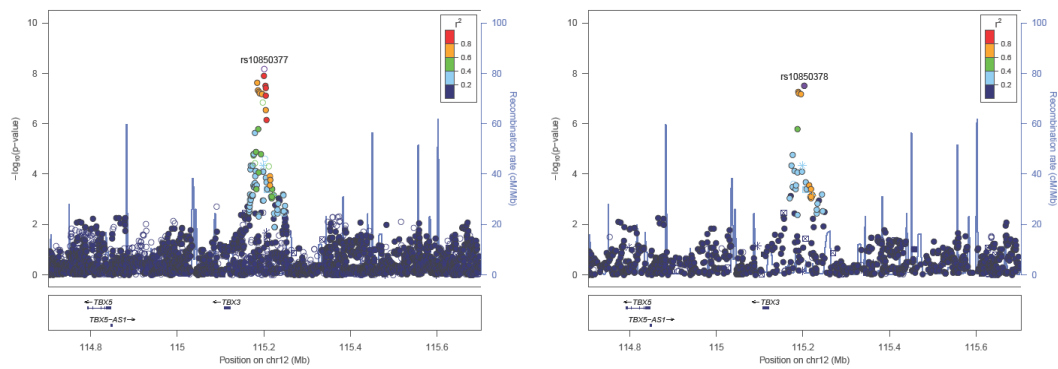
## viii. rs2274116



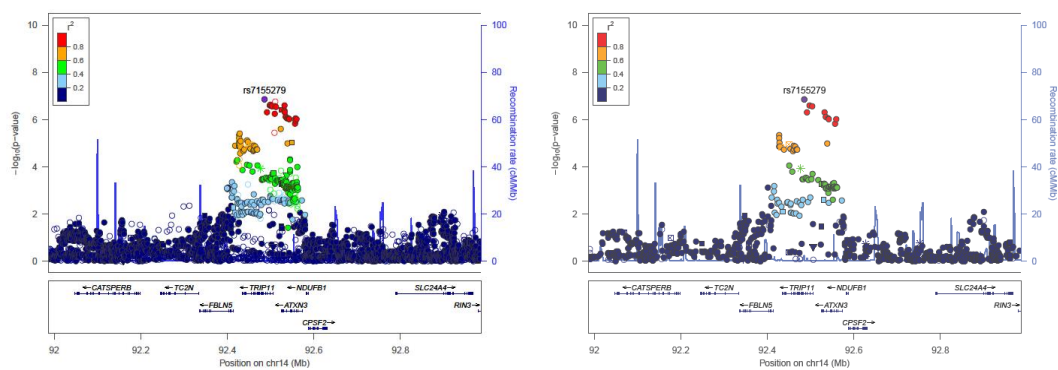
## ix. rs11383346 (chr12:28283187:I)



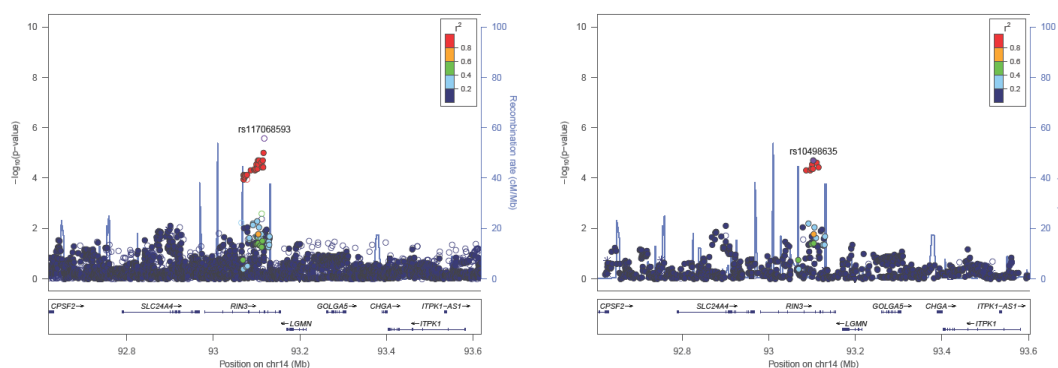
x. rs10850377



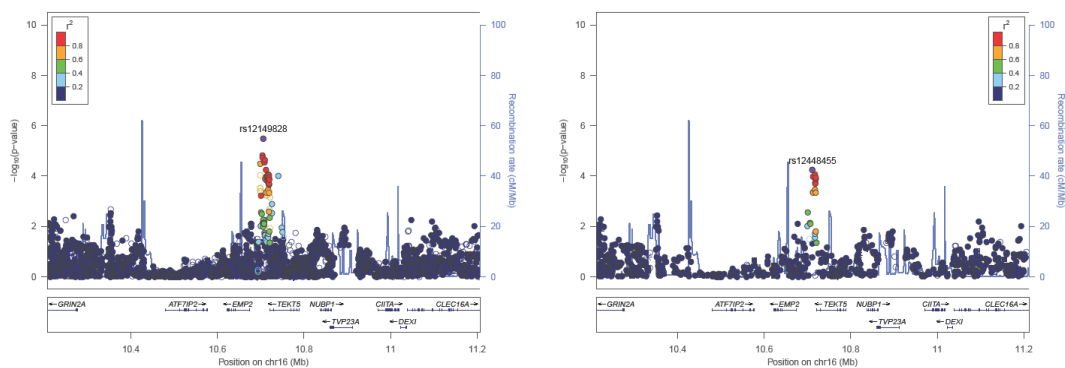
xi. rs7155279



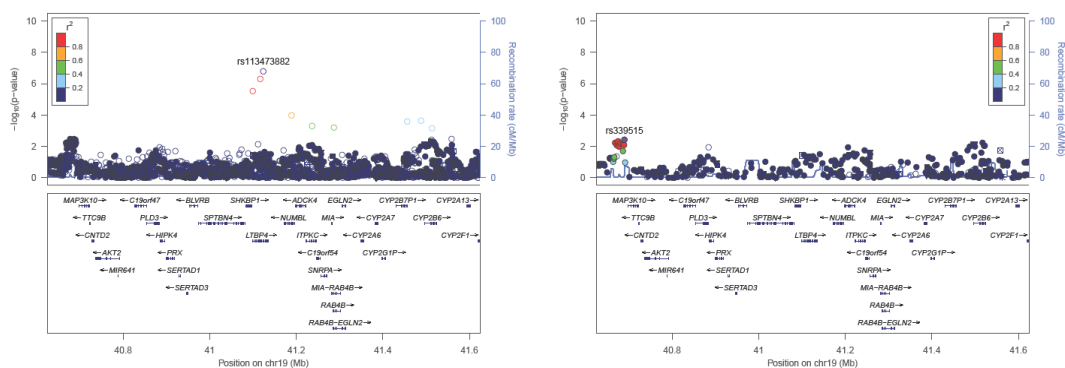
xii. rs117068593



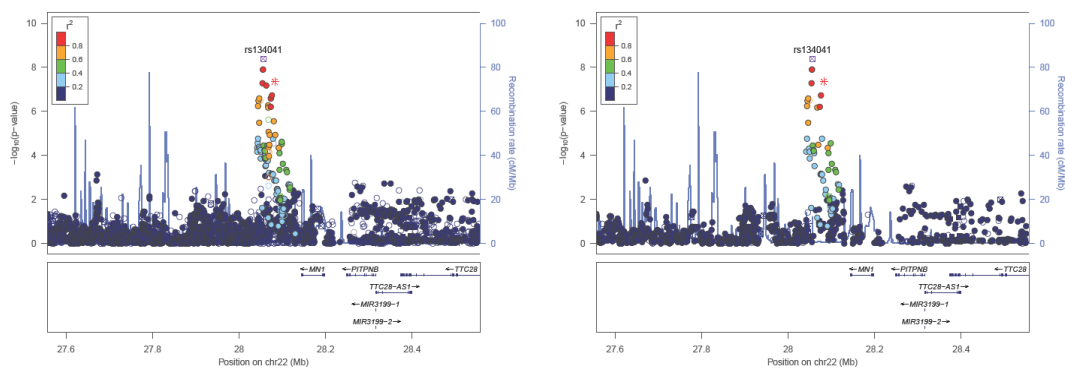
### xiii. rs12149828



### xiv. rs113473882



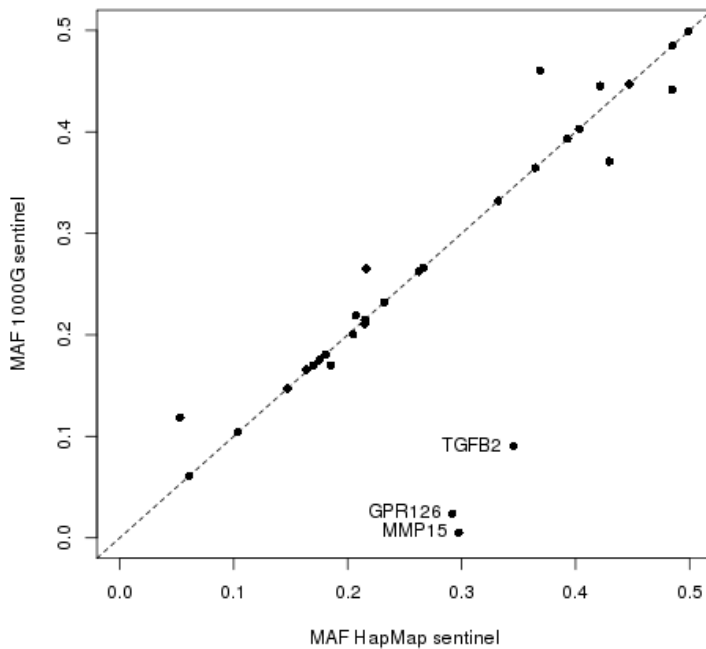
### xv. rs134041



Region plots are presented with the 1000 Genomes results including all 1000 Genomes variants with  $N$  effective  $\geq 70\%$  (plot on the left) and including only HapMap variants with  $N$  effective  $\geq 70\%$  extracted from the previous HapMap meta-analysis<sup>5</sup> (plot on the right) for all the new signals.

## b) Scatter plot of minor allele frequencies for HapMap sentinel variants vs. 1000

### Genomes sentinel variants



Shown are MAF for sentinel variants defined using 1000 Genomes stage 1 results vs. MAF for sentinel variants defined using 1000 Genomes stage 1 results restricted to HapMap variants only, in previously reported regions<sup>1-5</sup>, defined as the previously reported sentinel variant<sup>3,4</sup> +/- 500kb either side (*MFAP2*, *TGFB2*, *EFEMP1*, *TNS1*, *HDAC4*, *RARB*, *MECOM*, *FAM13A*, *GSTCD*, *HHIP*, *SPATA9*, *HTR4*, *ADAM19*, *BMP6*, *ZKSCAN3*, *NCR3*, *AGER*, *ARMC2*, *GPR126*, *PTCH1*, *CDC123*, *C10orf11*, *HSD17B12*, *PRDM11*, *LRP1*, *CCDC38*, *THSD4*, *MMP15*, *CFDP1*, *WWOX*, *KCNJ2*, *KCNE2*).

## **Supplementary Tables:**

**Supplementary Table 1** Sample population characteristics and genotyping platform details for each study in stage1 and stage2

a) Sample population characteristics for each study

Characteristics are shown for studies analysed in stage 1 (GWAS meta-analysis) and stage 2 (follow-up). Stage 1 studies: B58C (B58C-T1DGC, British 1958 Birth Cohort–Type 1 Diabetes Genetics Consortium and B58C-WTCCC, British 1958 Birth Cohort–Wellcome Trust Case Control Consortium); BHS1&2, Busselton Health Study 1 and 2; the CROATIA- Korcula study; the CROATIA-Split study; the CROATIA-Vis study; EPIC population based, European Prospective Investigation into Cancer and Nutrition Cohort; GS:SFHS, Generation Scotland: Scottish Family Health Study; H2000, Finnish Health 2000 survey; KORA F4, Cooperative Health Research in the Region of Augsburg; KORA S3, Cooperative Health Research in the Region of Augsburg; LBC1936, Lothian Birth Cohort 1936; NFBC1966, Northern Finland Birth Cohort of 1966; NSPHS, Northern Sweden Population Health Study; ORCADES, Orkney Complex Disease Study; SHIP, Study of Health in Pomerania; YFS, the Young Finish Study. Stage 2 studies: ECRHS, the European Community Respiratory Health Survey; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; the TwinsUK study; UK BiLEVE, UK Biobank Lung Exome Variant Evaluation study.

| Study name                | N Total | N male | N female | Age range (y) at lung function measurement | Mean age, y (s.d.) | Mean height, cm (s.d.) | Mean FEV <sub>1</sub> , L (s.d.) | Mean FVC, L (s.d.) | Mean FEV <sub>1</sub> /FVC (s.d.) | N never smokers | N ever smokers | Lambda FEV <sub>1</sub> | Lambda FVC | Lambda factor FEV <sub>1</sub> /FVC |
|---------------------------|---------|--------|----------|--------------------------------------------|--------------------|------------------------|----------------------------------|--------------------|-----------------------------------|-----------------|----------------|-------------------------|------------|-------------------------------------|
| <b>Stage 1</b>            |         |        |          |                                            |                    |                        |                                  |                    |                                   |                 |                |                         |            |                                     |
| B58C                      | 5934    | 2955   | 2979     | 44-45                                      | 45.12 (0.38)       | 169.43 (9.29)          | 3.30 (0.76)                      | 4.19 (0.98)        | 0.79 (0.08)                       | 1709            | 4225           | 1.022                   | 1.011      | 1.024                               |
| BHS1&2                    | 4355    | 1922   | 2433     | 17-97                                      | 51.21 (17.00)      | 168.00 (9.39)          | 3.01 (0.96)                      | 3.88 (1.16)        | 0.77 (0.07)                       | 2301            | 2054           | 1.015                   | 1.017      | 1.015                               |
| CROATIA-Korcula           | 826     | 302    | 524      | 18-90                                      | 55.63 (13.50)      | 168.10 (9.20)          | 2.72 (0.83)                      | 3.29 (0.96)        | 0.83 (0.1)                        | 403             | 423            | 1.003                   | 1.018      | 1.017                               |
| CROATIA-Split             | 493     | 210    | 283      | 18-85                                      | 49.08 (14.63)      | 172.60 (9.49)          | 3.19 (0.91)                      | 3.80 (1.06)        | 0.84 (0.08)                       | 239             | 254            | 1.003                   | 1.011      | 0.997                               |
| CROATIA-Vis               | 925     | 390    | 535      | 18-88                                      | 55.90 (15.51)      | 167.80 (9.88)          | 3.42 (1.21)                      | 4.41 (1.42)        | 0.77 (0.09)                       | 388             | 537            | 1.002                   | 0.982      | 0.969                               |
| EPIC population based     | 2339    | 1102   | 1237     | 39-77                                      | 59.20 (9.00)       | 167.10 (8.80)          | 2.50 (0.72)                      | 3.04 (0.90)        | 0.83 (0.11)                       | 1062            | 1277           | 1.005                   | 1.008      | 1.014                               |
| GS:SFHS                   | 8093    | 3385   | 4708     | 18-98                                      | 51.60 (13.34)      | 167.90 (9.55)          | 2.78 (0.87)                      | 3.91 (1.01)        | 0.71 (0.01)                       | 4319            | 3774           | 1.003                   | 1.014      | 1.013                               |
| H2000                     | 821     | 394    | 427      | 30-75                                      | 50.47 (10.91)      | 169.10 (9.14)          | 3.29 (0.9)                       | 4.16 (1.07)        | 0.79 (0.07)                       | 249             | 572            | 0.999                   | 1.002      | 1                                   |
| KORA F4                   | 1474    | 717    | 757      | 41-84                                      | 55.08 (9.90)       | 169.15 (9.42)          | 3.23 (0.85)                      | 4.19 (1.05)        | 0.77 (0.07)                       | 556             | 918            | 0.998                   | 1.003      | 1.008                               |
| KORA S3                   | 1147    | 551    | 596      | 28-89                                      | 50.82 (15.23)      | 169.22 (9.32)          | 3.34 (0.90)                      | 4.10 (1.06)        | 0.81 (0.08)                       | 520             | 627            | 1.009                   | 1.012      | 1.018                               |
| LBC1936                   | 991     | 501    | 490      | 68-71                                      | 69.55 (0.84)       | 166.44 (8.93)          | 2.38 (0.67)                      | 3.04 (0.87)        | 0.79 (0.10)                       | 437             | 554            | 1.011                   | 1.05       | 1.002                               |
| NFBC1966                  | 4563    | 2180   | 2383     | 31-31                                      | 31.00 (0)          | 171.00 (9.54)          | 3.93 (0.80)                      | 4.71 (0.99)        | 0.84 (0.07)                       | 1648            | 2915           | 1.005                   | 0.99       | 0.996                               |
| NSPHS                     | 871     | 400    | 471      | 14-91                                      | 49.20 (20.00)      | 164.00 (10.10)         | 2.92 (0.90)                      | 3.53 (1.06)        | 0.83 (0.09)                       | 750             | 121            | 0.996                   | 1.011      | 0.977                               |
| ORCADES                   | 1802    | 719    | 1083     | 16-91                                      | 54.00 (15.00)      | 166.00 (9.20)          | 2.89 (0.83)                      | 3.61 (0.99)        | 0.79 (0.08)                       | 1022            | 780            | 1.016                   | 1.013      | 1.009                               |
| SAPALDIA                  | 1378    | 665    | 713      | 18-61                                      | 41.30 (11.20)      | 169.47 (9.12)          | 3.53 (0.86)                      | 4.50 (1.04)        | 0.78 (0.08)                       | 631             | 747            | 0.995                   | 1.001      | 1.012                               |
| SHIP                      | 1768    | 863    | 905      | 25-85                                      | 52.43 (13.58)      | 169.66 (9.12)          | 3.28 (0.89)                      | 3.87 (1.03)        | 0.85 (0.06)                       | 770             | 998            | 1.019                   | 1.007      | 1.005                               |
| YFS                       | 419     | 198    | 221      | 30-47                                      | 38.88 (5.07)       | 172.25 (8.90)          | 3.73 (0.75)                      | 4.68 (0.99)        | 0.8 (0.06)                        | 233             | 186            | 1.012                   | 1.02       | 0.997                               |
| Total stage 1 sample size | 38199   |        |          |                                            |                    |                        |                                  |                    |                                   | 17237           | 20962          |                         |            |                                     |

| Study name                | N Total | N male | N female | Age range (y) at lung function measurement | Mean age, y (s.d.) | Mean height, cm (s.d.) | Mean FEV <sub>1</sub> , L (s.d.) | Mean FVC, L (s.d.) | Mean FEV <sub>1</sub> /FVC (s.d.) | N never smokers | N ever smokers | Lambda FEV <sub>1</sub> | Lambda FVC | Lambda factor FEV <sub>1</sub> /FVC |
|---------------------------|---------|--------|----------|--------------------------------------------|--------------------|------------------------|----------------------------------|--------------------|-----------------------------------|-----------------|----------------|-------------------------|------------|-------------------------------------|
| <b>Stage 2</b>            |         |        |          |                                            |                    |                        |                                  |                    |                                   |                 |                |                         |            |                                     |
| ECRHS                     | 1747    | 823    | 924      | 20-48                                      | 33.97 (7.16)       | 170.32 (9.47)          | 3.73 (0.82)                      | 4.54 (1.03)        | 0.82 (0.07)                       | 763             | 984            | NA                      | NA         | NA                                  |
| PIVUS                     | 837     | 406    | 431      | 70-72                                      | 70.20 (0.17)       | 168.93 (9.21)          | 2.44 (0.68)                      | 3.21 (0.87)        | 0.76 (0.10)                       | 409             | 428            | NA                      | NA         | NA                                  |
| TwinsUK                   | 3023    | 444    | 2579     | 19-82                                      | 53.08 (13.15)      | 161.68 (6.21)          | 2.63 (0.61)                      | 3.28 (0.65)        | 0.80 (0.08)                       | 1865            | 1158           | NA                      | NA         | NA                                  |
| UK BiLEVE                 | 48943   | 24489  | 24454    | 40-70                                      | 56.93 (7.89)       | 168.7 (9.13)           | 2.65 (0.87)                      | 3.59 (1.05)        | 0.73 (0.08)                       | 24483           | 24460          | NA                      | NA         | NA                                  |
| Total stage 2 sample size | 54550   |        |          |                                            |                    |                        |                                  |                    |                                   | 27520           | 27030          |                         |            |                                     |

b) Study, genotyping, imputation and genotype-phenotype data

Imp'n, imputation.

| Study name      | GWAS platform                                              | Calling algorithm                             | Individual call rate filter (applied before imp'n) | SNP call rate filter (applied before imp'n) | SNP HWE <i>P</i> filter (applied before imp'n)          | SNP MAF filter (applied before imp'n) | Other filters                                                                                                                                                                                   | No of SNPs after filtering (before imp'n) | Imputation software and version  | NCBI; 1000 Genomes version for imp'n                 | Genotype-phenotype association software |
|-----------------|------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------|---------------------------------------------|---------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|----------------------------------|------------------------------------------------------|-----------------------------------------|
| <b>Stage 1</b>  |                                                            |                                               |                                                    |                                             |                                                         |                                       |                                                                                                                                                                                                 |                                           |                                  |                                                      |                                         |
| B58C            | Illumina 550k/610k                                         | GenCall                                       | None                                               | >=95%                                       | $\geq 0.0001$ (tested on females only for chromosome X) | $\geq 1\%$                            | Consistent allele frequencies across data deposits ( $P \geq 0.0001$ for pairwise comparisons) and for chrX SNPs, consistent allele frequencies between males and females ( $P \geq 0.0001$ ).  | 500,521 (including 11,696 chrX)           | MACH 1.0.18 & Minimac 2012-11-16 | Phase 1 March 2012                                   | probABEL 0.1-9e                         |
| BHS1&2          | Illumina 610-Quad (N=1,168) & Illumina 660W-Quad (N=3,428) | BeadStudio (N=1,168) & GenomeStudio (N=3,428) | 0.95                                               | 0.95                                        | 1.00E-06                                                | 0.01                                  | Individuals were removed if they had sex inconsistencies, had heterozygosity > 5 s.d. from the mean, were PCA outliers, were 1 individual from a pair of duplicates or had IBD inconsistencies. | 521,307                                   | Minimac and MACH1 v1.0.18        | b37; Phase 1 March 2012                              | ProbABEL                                |
| CROATIA-Korcula | Illumina HumanHap370CNV duo chip                           | BeadStudio                                    | 97%                                                | 98%                                         | 1.00E-06                                                | 0.01                                  |                                                                                                                                                                                                 | 316,879                                   | SHAPEIT2, IMPUTE2                | b37; ALL (Phase 1 integrated release v3, April 2012) | ProbABEL                                |
| CROATIA-Split   | Illumina HumanHap370CNV quad chip                          | BeadStudio                                    | 97%                                                | 98%                                         | 1.00E-06                                                | 0.01                                  |                                                                                                                                                                                                 | 321,727                                   | SHAPEIT2, IMPUTE2                | b37; ALL (Phase 1 integrated release v3, April 2012) | ProbABEL                                |

| Study name            | GWAS platform                          | Calling algorithm   | Individual call rate filter (applied before imp'n) | SNP call rate filter (applied before imp'n) | SNP HWE <i>P</i> filter (applied before imp'n) | SNP MAF filter (applied before imp'n) | Other filters                                                                                                                                          | No of SNPs after filtering (before imp'n)                                                          | Imputation software and version | NCBI; 1000 Genomes version for imp'n                                                                        | Genotype-phenotype association software |
|-----------------------|----------------------------------------|---------------------|----------------------------------------------------|---------------------------------------------|------------------------------------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| CROATIA-Vis           | Illumina Infinium HumanHap300 BeadChip | BeadStudio          | 97%                                                | 98%                                         | 1.00E-06                                       | 0.01                                  |                                                                                                                                                        | 273,671                                                                                            | SHAPEIT2, IMPUTE2               | b37; ALL (Phase 1 integrated release v3, April 2012)                                                        | ProbABEL                                |
| EPIC population based | Affymetrix 500K                        | BRLMM               | 94%                                                | 90%                                         | 1.00E-06                                       | 0.01                                  | Heterozygosity, ethnic outlier                                                                                                                         | 392,573                                                                                            | IMPUTE 2.2.2                    | Mar-12                                                                                                      | SNPTEST 2.4.0                           |
| GS:SFHS               | Illumina OmniExpress+Exome             | GenomeStudio        | 97% (Omni); 99% (Exome)                            | 98%                                         | 1.00E-06                                       | 0.01 (Omni); 0.0001 (Exome)           |                                                                                                                                                        | 690,759                                                                                            | SHAPEIT2, IMPUTE2               | b37; ALL (Phase 1 integrated release v3, April 2012)                                                        | ProbABEL                                |
| H2000                 | Illumina HumanHap 610K                 | Illuminus           | 0.95                                               | 0.95 (0.99 for SNPs with MAF < 0.05)        | 1.00E-06                                       | 0.01                                  |                                                                                                                                                        | 553,722                                                                                            | IMPUTE version 2.2.2            | 1,000 Genomes haplotypes -- Phase I integrated variant set release (v3) in NCBI build 37 (hg19) coordinates | SNPTest                                 |
| KORA F4               | Affymetrix Axiom                       | Affymetrix Software | 0.97                                               | 0.98                                        | 5x10 <sup>-6</sup>                             | 0.01                                  | -mismatch of phenotypic and genetic gender<br>- 5s.d. from mean heterozygosity rate<br>- check for European ancestry<br>- check for population outlier | 523,260 (chr 1-26)<br>508,532 (chr 1-22)<br>14,096(chrX-nonPAR)<br>444(chrX-PAR1)<br>58(chrX-PAR2) | SHAPEIT v2, IMPUTE v2.3.0       | 1000g phase1 all (ALL_1000G_phase1integrated_v3_impute_mac1)                                                | SNPTEST v2.4.1                          |

| Study name | GWAS platform                                               | Calling algorithm                                 | Individual call rate filter (applied before imp'n) | SNP call rate filter (applied before imp'n) | SNP HWE <i>P</i> filter (applied before imp'n) | SNP MAF filter (applied before imp'n) | Other filters                                                                                                                                                                                                                                   | No of SNPs after filtering (before imp'n)                     | Imputation software and version | NCBI; 1000 Genomes version for imp'n                         | Genotype-phenotype association software |
|------------|-------------------------------------------------------------|---------------------------------------------------|----------------------------------------------------|---------------------------------------------|------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------|--------------------------------------------------------------|-----------------------------------------|
| KORA S3    | Illumina Omni 2.5/ Illumina Omni Express                    | Genome Studio                                     | 0.97                                               | 0.98                                        | 5x10 <sup>-6</sup>                             | 0.01                                  | person wise: - mismatch of phenotypic and genetic gender<br>- 5s.d. from mean heterozygosity rate<br>- check for European ancestry<br>- check for population outlier<br>SNP wise: only SNPs that were genotyped with good quality on both chips | 600641 (chr 1-26)<br>588307 (chr 1-22)<br>14625 (chrX-nonPAR) | SHAPEIT v2, IMPUTE v2.3.0       | 1000g phase1 all (ALL_1000G_phase1integrated_v3_impute_mac1) | SNPTEST v2.4.1                          |
| LBC1936    | Illumina 610-Quadv1                                         | GenomeStudio                                      | 0.95                                               | 0.98                                        | ≥0.001                                         | 0.01                                  |                                                                                                                                                                                                                                                 | 549,692                                                       | minimac 2012-11-16              | version 3, cosmopolitan                                      | mach2qtl                                |
| NFBC1966   | Illumina HumanCN V-370DUO Analysis BeadChip                 | Beadstudio                                        | 95%                                                | 95 % (99 % if MAF < 5 % )                   | 1.00E-04                                       | 0.01                                  | Duplicates concordance < 99%; IBS pairwise sharing>0.20; withdrew consent; gender mismatch; heterozygosity outliers>0.29; MDS outliers.                                                                                                         | 309,948                                                       | Impute version 2.3.0            | 1000G March 2012 pphase1 integrated v3                       | SNPTEST                                 |
| NSPHS      | Illumina Infinum HapMap 300 v2 & Illumina Human OmniExpress | BeadStudio (Infinum) & Genomestudio (OmniExpress) | 0.9                                                | 0.95                                        | 3.2E-08 (Infinum) & 1.4E-08 (OmniExpress)      | 0.01                                  | FDR level of heterozygosity 0.01                                                                                                                                                                                                                | 306,086 (Infinum) & 631503 (OmniExpress)                      | Impute2 (v 2.2.2)               | hg19                                                         | ProbABEL                                |

| Study name | GWAS platform                                    | Calling algorithm                                                                                             | Individual call rate filter (applied before imp'n) | SNP call rate filter (applied before imp'n) | SNP HWE <i>P</i> filter (applied before imp'n) | SNP MAF filter (applied before imp'n)    | Other filters                                                           | No of SNPs after filtering (before imp'n)        | Imputation software and version                                                                            | NCBI; 1000 Genomes version for imp'n                                                                | Genotype-phenotype association software |
|------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------|---------------------------------------------|------------------------------------------------|------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------|
| ORCADES    | Illumina Hap300, Illumina Omni1 & Illumina OmniX | Beadstudio using Hap300v2 cluster file (Hap300) & Genome Studio, using Illumina cluster files (Omni1 & OmniX) | 98%                                                | 97%                                         | 1.00E-06                                       | 1% (Hap300) & monomorphic (Omni & OmniX) | Subject Heterozygosity FDR<1%                                           | 287,208 (Hap300), 843723 (Omni) & 654651 (OmniX) | shapeit.v2.r644.+impute_v2.2.2_x86_64_static/impute2                                                       | 1000G Phase I Integrated Release Version 3 Haplotypes (2010-11 data freeze, 2012-03-14 haplotypes). | probABEL v. 0.4.3                       |
| SAPALDIA   | Illumina 610k quad                               | Gencall                                                                                                       | 95%                                                | 95%                                         | 1.00E-06                                       | 0.01                                     | none                                                                    | 545,131                                          | Mach 1.0.16.a, minimac-omp RELEASE STAMP 2012-05-29 (autosomes) & MiniMac RELEASE STAMP 2012-11-16 (chr X) | build37                                                                                             | probABEL                                |
| SHIP       | Affymetrix SNP 6.0                               | Birdseed2                                                                                                     | >92%                                               | >80%                                        | >0.0001                                        | none                                     | duplicate SNP positions, sex-mismatch or duplicate individuals (by IBD) | 905,910                                          | IMPUTE v2.2.2                                                                                              | b37, 1000Gv3 (Mar 2012)                                                                             | QUICKTEST v0.95                         |
| YFS        | Illumina 670k custom                             | Illuminus                                                                                                     | 0.95                                               | 0.95                                        | 1.00E-06                                       | 0.01                                     | heterozygosity, relatedness                                             | 546,674                                          | SHAPEIT v1 and IMPUTE v2.2.2                                                                               | Phase 1, release v3, March 2012 haplotypes                                                          | SNPTEST v.2.4.1                         |

| Study name     | GWAS platform                              | Calling algorithm                                     | Individual call rate filter (applied before imp'n) | SNP call rate filter (applied before imp'n) | SNP HWE <i>P</i> filter (applied before imp'n) | SNP MAF filter (applied before imp'n) | Other filters                                                                | No of SNPs after filtering (before imp'n)    | Imputation software and version | NCBI; 1000 Genomes version for imp'n | Genotype-phenotype association software |
|----------------|--------------------------------------------|-------------------------------------------------------|----------------------------------------------------|---------------------------------------------|------------------------------------------------|---------------------------------------|------------------------------------------------------------------------------|----------------------------------------------|---------------------------------|--------------------------------------|-----------------------------------------|
| <b>Stage 2</b> |                                            |                                                       |                                                    |                                             |                                                |                                       |                                                                              |                                              |                                 |                                      |                                         |
| ECRHS          | Human 610 Quad Chip (ILLUMINA)             | BeadStudio                                            | exclusion of males with high X heterozygosity      | 95%                                         | 0.0001                                         | 1%                                    | sex discrepancies, IBS analysis for relatedness, ancestry analysis using PCA | 567,512                                      | IMPUTE2                         | version 3                            | SNPTEST v2                              |
| PIVUS          | Illumina OmniExpress and Metabocchip       | Bead Studio                                           | ≥0.95                                              | ≥0.95 (≥0.99 for MAF<0.05)                  | 10 <sup>-6</sup>                               | ≥0.01                                 |                                                                              | 738,606                                      | SHAPEIT and IMPUTE2             | Mar-12                               | SNPTEST                                 |
| TwinsUK        | Illumina 300K Duo for and HumanHap610-Quad |                                                       | Illumina GenCall                                   | if MAF>5% then 0.95, else 0.99              | E-06                                           | 1%                                    |                                                                              | unavailable                                  | Impute 2                        | Mar-12                               | Gemma                                   |
| UK BiLEVE      | Affymetrix Axiom UK BiLEVE array           | Axiom® GT1 algorithm (Affymetrix Power Tools v1.15.1) | 95%                                                | None                                        | 1.00E-06                                       | 1%                                    | Het. outliers, PCA outliers, sex mismatch, relateds (IBD)                    | unavailable (regional imputation undertaken) | SHAPEIT and IMPUTE2             | Mar-12                               | SNPTEST                                 |

## Supplementary Table 2 Follow-up results

### a) Association results for 56 variants followed up in stage 2

Results for stage 1, stage 2 and the meta-analysis of both are presented for the 56 variants (55 from autosomal chromosomes and 1 from chromosome X) followed up in stage 2.  $P < 5 \times 10^{-8}$  after meta-analysing stage 1 and stage 2 are highlighted in bold. rs189059189 and rs117068593 appear twice on the table because they were selected for follow-up for two different traits. Chr., chromosome; dist., distance.

| rs number (chr: position)    | Gene (function)                                   | Measure               | Coded allele/ Non coded allele | Stage 1 |       |          | Stage 2 |       |          | Stage 1 + stage 2 |       |                 |
|------------------------------|---------------------------------------------------|-----------------------|--------------------------------|---------|-------|----------|---------|-------|----------|-------------------|-------|-----------------|
|                              |                                                   |                       |                                | Beta    | SE    | P        | Beta    | SE    | P        | Beta              | SE    | P               |
| rs10798992 (chr1:34268324)   | CSMD2 (intronic)                                  | FEV <sub>1</sub> /FVC | C/A                            | 0.041   | 0.008 | 1.25E-07 | 0.002   | 0.006 | 7.14E-01 | 0.017             | 0.005 | 3.02E-04        |
| rs4658231 (chr1:92041502)    | CDC7 (dist=50181), TGFBR3 (dist=104398)           | FVC                   | A/G                            | 0.051   | 0.009 | 5.33E-09 | 0.011   | 0.007 | 1.20E-01 | 0.027             | 0.006 | 8.36E-07        |
| rs2764553 (chr1:111732303)   | DENND2D (intronic)                                | FEV <sub>1</sub> /FVC | C/A                            | 0.044   | 0.010 | 3.73E-06 | 0.020   | 0.008 | 7.27E-03 | 0.030             | 0.006 | 6.37E-07        |
| rs4926386 (chr1:149886135)   | SV2A (intronic)                                   | FEV <sub>1</sub>      | C/A                            | -0.062  | 0.012 | 1.99E-07 | -0.030  | 0.010 | 3.58E-03 | -0.044            | 0.008 | <b>2.09E-08</b> |
| rs6681426 (chr1:150586971)   | MCL1 (dist=34757), ENSA (dist=7628)               | FEV <sub>1</sub>      | G/A                            | 0.042   | 0.008 | 1.07E-07 | 0.021   | 0.006 | 1.13E-03 | 0.029             | 0.005 | <b>4.35E-09</b> |
| rs201204531 (chr1:219963090) | LYPLAL1 (dist=576883), RNU5F-1 (dist=83529)       | FEV <sub>1</sub> /FVC | A/ATG                          | -0.038  | 0.008 | 1.98E-06 | -0.027  | 0.006 | 1.77E-05 | -0.031            | 0.005 | <b>2.68E-10</b> |
| rs61067109 (chr2:18292452)   | KCNS3 (dist=178227), NT5C1B-RDH14 (dist=443537)   | FEV <sub>1</sub> /FVC | G/A                            | -0.050  | 0.009 | 3.09E-08 | -0.042  | 0.007 | 6.56E-09 | -0.045            | 0.006 | <b>1.40E-15</b> |
| rs1080871 (chr2:46854708)    | CRIPT (UTR3)                                      | FEV <sub>1</sub> /FVC | A/G                            | 0.035   | 0.008 | 4.79E-06 | 0.007   | 0.006 | 2.38E-01 | 0.018             | 0.005 | 1.56E-04        |
| rs13386197 (chr2:47798588)   | KCNK12 (dist=1118), MSH6 (dist=211633)            | FVC                   | C/G                            | 0.096   | 0.020 | 1.65E-06 | 0.011   | 0.014 | 4.44E-01 | 0.039             | 0.011 | 7.48E-04        |
| rs185216854 (chr2:119211347) | INSIG2 (dist=343750), LOC101927709 (dist=146012)  | FEV <sub>1</sub> /FVC | G/T                            | 0.180   | 0.037 | 1.31E-06 | -0.029  | 0.030 | 3.38E-01 | 0.055             | 0.024 | 1.99E-02        |
| rs74445319 (chr2:181515383)  | CWC22 (dist=643603), SCHLAP1 (dist=41448)         | FVC                   | C/T                            | 0.102   | 0.022 | 4.68E-06 | 0.021   | 0.014 | 1.49E-01 | 0.044             | 0.012 | 2.23E-04        |
| rs11432697 (chr3:89210365)   | EPHA3 (intronic)                                  | FVC                   | T/TA                           | 0.042   | 0.009 | 4.05E-06 | 0.018   | 0.007 | 1.75E-02 | 0.027             | 0.006 | 1.97E-06        |
| rs10935473 (chr3:98416900)   | CPOX (dist=104445), ST3GAL6-AS1 (dist=16277)      | FVC                   | G/T                            | -0.038  | 0.008 | 4.87E-06 | -0.007  | 0.006 | 2.76E-01 | -0.018            | 0.005 | 3.37E-04        |
| rs7356112 (chr3:143970905)   | C3orf58 (dist=259695), PLOD2 (dist=1816323)       | FVC                   | C/T                            | 0.104   | 0.021 | 6.05E-07 | 0.011   | 0.015 | 4.83E-01 | 0.044             | 0.012 | 4.24E-04        |
| rs6441207 (chr3:158282459)   | RP11-538P18.2 (ncRNA intronic)                    | FVC                   | C/T                            | 0.036   | 0.008 | 4.54E-06 | 0.036   | 0.006 | 5.85E-09 | 0.036             | 0.005 | <b>1.27E-13</b> |
| rs73223499 (chr4:14300501)   | LINC01085 (dist=158825), CPEB2-AS1 (dist=611084)  | FEV <sub>1</sub> /FVC | C/T                            | -0.080  | 0.017 | 3.99E-06 | -0.037  | 0.015 | 1.42E-02 | -0.055            | 0.011 | 1.15E-06        |
| rs35288667 (chr4:16544514)   | LDB2 (intronic)                                   | FVC                   | A/G                            | 0.049   | 0.010 | 1.55E-06 | -0.005  | 0.008 | 5.01E-01 | 0.015             | 0.006 | 1.81E-02        |
| rs6856422 (chr4:106841962)   | NPNT (intronic)                                   | FEV <sub>1</sub> /FVC | G/T                            | -0.044  | 0.008 | 1.30E-07 | -0.055  | 0.006 | 1.15E-17 | -0.051            | 0.005 | <b>1.51E-23</b> |
| rs11269742 (chr4:177758035)  | VEGFC (dist=44136), NEIL3 (dist=472956)           | FVC                   | T/TGGGA<br>AAAAAAT<br>AC       | 0.043   | 0.009 | 9.91E-07 | 0.000   | 0.007 | 9.78E-01 | 0.017             | 0.005 | 2.19E-03        |
| rs112226333 (chr5:31525207)  | DROSHA (intronic)                                 | FEV <sub>1</sub>      | G/T                            | 0.051   | 0.010 | 6.12E-07 | 0.016   | 0.008 | 4.42E-02 | 0.029             | 0.006 | 3.32E-06        |
| rs11960365 (chr5:79650724)   | CRSP8P (dist=2939), ZFYVE16 (dist=53108)          | FVC                   | G/T                            | 0.050   | 0.010 | 2.15E-06 | -0.008  | 0.008 | 3.30E-01 | 0.014             | 0.006 | 3.25E-02        |
| rs149178928 (chr5:106109235) | RAB9BP1 (dist=1673436), LOC102467213 (dist=41663) | FEV <sub>1</sub>      | G/A                            | 0.132   | 0.027 | 1.14E-06 | 0.018   | 0.021 | 3.82E-01 | 0.060             | 0.016 | 2.57E-04        |
| rs114372586 (chr6:32886487)  | LOC100294145 (dist=14952), HLA-DMB (dist=15919)   | FVC                   | T/C                            | 0.081   | 0.017 | 2.83E-06 | 0.019   | 0.012 | 1.20E-01 | 0.040             | 0.010 | 7.30E-05        |

| rs number (chr: position)    | Gene (function)                                               | Measure               | Coded allele/ Non coded allele | Stage 1 |       |          | Stage 2 |       |          | Stage 1 + stage 2 |       |                 |
|------------------------------|---------------------------------------------------------------|-----------------------|--------------------------------|---------|-------|----------|---------|-------|----------|-------------------|-------|-----------------|
|                              |                                                               |                       |                                | Beta    | SE    | P        | Beta    | SE    | P        | Beta              | SE    | P               |
| rs79787160 (chr6:72212515)   | <i>LINC00472</i> (dist=82067),<br><i>RIMS1</i> (dist=383891)  | FEV <sub>1</sub> /FVC | A/G                            | 0.241   | 0.050 | 1.09E-06 | 0.020   | 0.038 | 5.93E-01 | 0.103             | 0.030 | 6.71E-04        |
| rs9352253 (chr6:76687328)    | <i>IMPG1</i> (intronic)                                       | FEV <sub>1</sub>      | A/C                            | 0.041   | 0.009 | 1.51E-06 | -0.012  | 0.007 | 7.25E-02 | 0.008             | 0.005 | 1.25E-01        |
| rs148274477 (chr6:142838173) | <i>GPR126</i> (dist=70770), <i>RP11-440G9.1</i> (dist=9419)   | FEV <sub>1</sub> /FVC | C/T                            | -0.161  | 0.027 | 2.68E-09 | -0.162  | 0.019 | 5.63E-18 | -0.162            | 0.015 | <b>9.58E-26</b> |
| rs6570551 (chr6:143556810)   | <i>AIG1</i> (intronic)                                        | FEV <sub>1</sub> /FVC | A/G                            | -0.042  | 0.008 | 7.67E-08 | -0.001  | 0.006 | 9.11E-01 | -0.017            | 0.005 | 4.62E-04        |
| rs4728570 (chr7:84728349)    | <i>SEMA3D</i> (intronic)                                      | FEV <sub>1</sub>      | G/A                            | -0.037  | 0.008 | 3.06E-06 | -0.006  | 0.006 | 3.45E-01 | -0.018            | 0.005 | 2.80E-04        |
| rs141779646 (chr7:90805723)  | <i>CDK14</i> (intronic)                                       | FVC                   | G/C                            | 0.087   | 0.019 | 3.80E-06 | -0.016  | 0.016 | 3.23E-01 | 0.028             | 0.012 | 2.40E-02        |
| rs112225874 (chr8:69228553)  | <i>LOC286189</i> (ncRNA intronic)                             | FVC                   | C/T                            | 0.114   | 0.025 | 3.84E-06 | 0.032   | 0.024 | 1.72E-01 | 0.071             | 0.017 | 2.82E-05        |
| rs76163270 (chr9:24678364)   | <i>IZUMO3</i> (dist=132690),<br><i>TUSC1</i> (dist=998023)    | FEV <sub>1</sub> /FVC | A/C                            | -0.079  | 0.017 | 4.65E-06 | -0.018  | 0.014 | 1.80E-01 | -0.042            | 0.011 | 9.64E-05        |
| rs34886460 (chr9:119359372)  | <i>ASTN2</i> (intronic)                                       | FEV <sub>1</sub> /FVC | T/TA                           | 0.041   | 0.008 | 6.75E-08 | 0.025   | 0.006 | 4.07E-05 | 0.031             | 0.005 | <b>4.72E-11</b> |
| rs2274116 (chr9:139094805)   | <i>LHX3</i> (exonic)                                          | FVC                   | C/T                            | 0.041   | 0.009 | 2.68E-06 | 0.038   | 0.007 | 4.20E-09 | 0.039             | 0.005 | <b>5.55E-14</b> |
| rs10735064 (chr12:888848)    | <i>WNK1</i> (intronic)                                        | FVC                   | G/A                            | 0.042   | 0.009 | 3.49E-06 | 0.014   | 0.007 | 5.41E-02 | 0.025             | 0.006 | 1.03E-05        |
| rs12314259 (chr12:12272466)  | <i>LRP6</i> (UTR3)                                            | FVC                   | C/G                            | 0.048   | 0.010 | 4.67E-06 | -0.002  | 0.009 | 8.29E-01 | 0.018             | 0.007 | 6.46E-03        |
| rs11383346 (chr12:28283187)  | <i>PTHLH</i> (dist=158271),<br><i>CCDC91</i> (dist=126946)    | FVC                   | A/AT                           | -0.043  | 0.008 | 3.83E-08 | -0.041  | 0.006 | 4.42E-11 | -0.042            | 0.005 | <b>9.52E-18</b> |
| rs10850377 (chr12:115201436) | <i>TBX3</i> (dist=79467),<br><i>MED13L</i> (dist=1194945)     | FEV <sub>1</sub>      | G/A                            | -0.047  | 0.008 | 6.68E-09 | -0.028  | 0.006 | 1.55E-05 | -0.035            | 0.005 | <b>2.50E-12</b> |
| rs6563127 (chr13:80216147)   | <i>NDFIP2</i> (dist=85935),<br><i>LINC01080</i> (dist=369065) | FVC                   | A/G                            | -0.059  | 0.013 | 2.91E-06 | -0.011  | 0.011 | 3.38E-01 | -0.031            | 0.008 | 1.46E-04        |
| rs189059189 (chr14:34231304) | <i>NPAS3</i> (intronic)                                       | FEV <sub>1</sub>      | C/T                            | -0.355  | 0.067 | 1.11E-07 | -0.035  | 0.051 | 4.99E-01 | -0.154            | 0.041 | 1.61E-04        |
| rs189059189 (chr14:34231304) | <i>NPAS3</i> (intronic)                                       | FVC                   | C/T                            | -0.318  | 0.067 | 2.19E-06 | -0.041  | 0.051 | 4.23E-01 | -0.143            | 0.041 | 4.46E-04        |
| rs61980882 (chr14:75021464)  | <i>LTBP2</i> (intronic)                                       | FVC                   | C/T                            | -0.039  | 0.008 | 3.72E-07 | -0.007  | 0.006 | 2.22E-01 | -0.020            | 0.005 | 3.65E-05        |
| rs7155279 (chr14:92485881)   | <i>TRIP11</i> (intronic)                                      | FEV <sub>1</sub>      | G/T                            | -0.041  | 0.008 | 1.39E-07 | -0.022  | 0.006 | 4.17E-04 | -0.030            | 0.005 | <b>1.41E-09</b> |
| rs117068593 (chr14:93118229) | <i>RIN3</i> (exonic)                                          | FEV <sub>1</sub>      | C/T                            | -0.048  | 0.010 | 2.72E-06 | -0.027  | 0.008 | 5.68E-04 | -0.035            | 0.006 | <b>2.25E-08</b> |
| rs117068593 (chr14:93118229) | <i>RIN3</i> (exonic)                                          | FVC                   | C/T                            | -0.054  | 0.010 | 1.74E-07 | -0.022  | 0.008 | 5.83E-03 | -0.033            | 0.006 | 8.10E-08        |
| rs4906032 (chr14:101518910)  | <i>MIR381HG</i> , <i>MIR487A</i> (downstream)                 | FVC                   | A/G                            | 0.037   | 0.008 | 4.78E-06 | 0.004   | 0.007 | 5.75E-01 | 0.018             | 0.005 | 7.31E-04        |
| rs8027068 (chr15:100339709)  | <i>DNM1P46</i> (ncRNA intronic)                               | FEV <sub>1</sub> /FVC | G/A                            | 0.043   | 0.009 | 3.79E-06 | -0.005  | 0.007 | 5.05E-01 | 0.012             | 0.006 | 2.97E-02        |
| rs113733630 (chr16:4343067)  | <i>TFAP4</i> (dist=20066), <i>GLIS2</i> (dist=39158)          | FEV <sub>1</sub> /FVC | A/AGTTT                        | 0.042   | 0.009 | 3.78E-06 | 0.015   | 0.007 | 4.03E-02 | 0.025             | 0.006 | 6.92E-06        |
| rs12149828 (chr16:10706328)  | <i>EMP2</i> (dist=31789), <i>TEKT5</i> (dist=15033)           | FEV <sub>1</sub> /FVC | G/A                            | 0.049   | 0.010 | 3.16E-06 | 0.035   | 0.008 | 3.33E-05 | 0.040             | 0.007 | <b>7.65E-10</b> |
| rs12929007 (chr16:30929696)  | <i>FBXL19-AS1</i> (downstream)                                | FEV <sub>1</sub>      | C/G                            | -0.049  | 0.010 | 6.21E-07 | 0.001   | 0.007 | 8.47E-01 | -0.016            | 0.006 | 5.95E-03        |
| rs7187961 (chr16:53826034)   | <i>FTO</i> (intronic)                                         | FVC                   | T/C                            | 0.048   | 0.010 | 3.43E-06 | -0.008  | 0.007 | 2.80E-01 | 0.011             | 0.006 | 6.76E-02        |
| rs16953104 (chr16:54165373)  | <i>FTO</i> (dist=16994), <i>IRX3</i> (dist=151839)            | FEV <sub>1</sub>      | C/T                            | 0.276   | 0.057 | 1.09E-06 | -0.007  | 0.064 | 9.10E-01 | 0.152             | 0.042 | 3.35E-04        |

| rs number (chr: position)    | Gene (function)                        | Measure               | Coded allele/ Non coded allele | Stage 1 |       |          | Stage 2 |       |          | Stage 1 + stage 2 |       |                 |
|------------------------------|----------------------------------------|-----------------------|--------------------------------|---------|-------|----------|---------|-------|----------|-------------------|-------|-----------------|
|                              |                                        |                       |                                | Beta    | SE    | P        | Beta    | SE    | P        | Beta              | SE    | P               |
| rs4792721 (chr17:16006827)   | NCOR1 (intronic)                       | FEV <sub>1</sub>      | A/G                            | 0.038   | 0.008 | 1.67E-06 | 0.017   | 0.006 | 8.06E-03 | 0.025             | 0.005 | 4.42E-07        |
| rs58270905 (chr18:42844617)  | SLC14A2 (intronic)                     | FEV <sub>1</sub> /FVC | A/G                            | 0.252   | 0.055 | 4.51E-06 | 0.013   | 0.049 | 7.92E-01 | 0.118             | 0.036 | 1.20E-03        |
| rs34000248 (chr18:67464012)  | DOK6 (intronic)                        | FEV <sub>1</sub>      | ACT/A                          | -0.070  | 0.014 | 5.75E-07 | 0.012   | 0.012 | 3.18E-01 | -0.023            | 0.009 | 1.11E-02        |
| rs113473882 (chr19:41124155) | LTBP4 (intronic)                       | FEV <sub>1</sub> /FVC | T/C                            | -0.174  | 0.033 | 1.48E-07 | -0.138  | 0.028 | 1.00E-06 | -0.153            | 0.021 | <b>9.95E-13</b> |
| rs134041 (chr22:28056338)    | MIAT (dist=983898), MN1 (dist=87927)   | FEV <sub>1</sub>      | T/C                            | -0.045  | 0.008 | 4.19E-09 | -0.018  | 0.006 | 4.19E-03 | -0.028            | 0.005 | <b>3.03E-09</b> |
| rs79017381 (chr22:31496200)  | SMTN (intronic)                        | FEV <sub>1</sub> /FVC | C/T                            | 0.120   | 0.026 | 4.41E-06 | 0.026   | 0.019 | 1.71E-01 | 0.059             | 0.015 | 1.36E-04        |
| rs7050036 (chrX:15964845)    | AP1S2 (dist=91708), GRPR (dist=176579) | FEV <sub>1</sub> /FVC | T/A                            | -0.041  | 0.007 | 4.37E-09 | -0.013  | 0.005 | 1.60E-02 | -0.023            | 0.004 | 4.14E-08        |

b) Association results for FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and FVC for the 16 sentinel variants

Results for FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and FVC in stage 1, stage 2 and the meta-analysis of both are presented for the 16 sentinel variants.  $P < 5 \times 10^{-8}$  after meta-analysing stage 1 and stage 2 are highlighted in bold. Chr., chromosome; dist., distance.

| rs number (chr: position)       | Gene (function)                                                  | Measure               | Coded allele/ Non coded allele | Stage 1 |       |          | Stage 2 |       |          | Stage 1 + stage 2 |       |                 |
|---------------------------------|------------------------------------------------------------------|-----------------------|--------------------------------|---------|-------|----------|---------|-------|----------|-------------------|-------|-----------------|
|                                 |                                                                  |                       |                                | Beta    | SE    | P        | Beta    | SE    | P        | Beta              | SE    | P               |
| rs6681426<br>(chr1:150586971)   | <i>MCL1</i> (dist=34757), <i>ENSA</i> (dist=7628)                | FEV <sub>1</sub>      | G/A                            | 0.042   | 0.008 | 1.07E-07 | 0.021   | 0.006 | 1.13E-03 | 0.029             | 0.005 | <b>4.35E-09</b> |
|                                 |                                                                  | FEV <sub>1</sub> /FVC | G/A                            | 0.014   | 0.008 | 7.47E-02 | -0.003  | 0.006 | 6.17E-01 | 0.004             | 0.005 | 4.65E-01        |
|                                 |                                                                  | FVC                   | G/A                            | 0.036   | 0.008 | 4.74E-06 | 0.024   | 0.006 | 1.42E-04 | 0.029             | 0.005 | <b>5.56E-09</b> |
| rs201204531<br>(chr1:219963090) | <i>LYPLAL1</i> (dist=576883), <i>RNU5F-1</i><br>(dist=83529)     | FEV <sub>1</sub>      | A/ATG                          | -0.007  | 0.008 | 3.75E-01 | -0.017  | 0.006 | 7.49E-03 | -0.013            | 0.005 | 8.09E-03        |
|                                 |                                                                  | FEV <sub>1</sub> /FVC | A/ATG                          | -0.038  | 0.008 | 1.98E-06 | -0.027  | 0.006 | 1.77E-05 | -0.031            | 0.005 | <b>2.68E-10</b> |
|                                 |                                                                  | FVC                   | A/ATG                          | 0.011   | 0.008 | 1.53E-01 | -0.008  | 0.006 | 2.18E-01 | 0.000             | 0.005 | 9.31E-01        |
| rs61067109<br>(chr2:18292452)   | <i>KCNS3</i> (dist=178227), <i>NT5C1B-RDH14</i><br>(dist=443537) | FEV <sub>1</sub>      | G/A                            | -0.039  | 0.009 | 1.83E-05 | -0.036  | 0.007 | 3.93E-07 | -0.037            | 0.006 | <b>3.21E-11</b> |
|                                 |                                                                  | FEV <sub>1</sub> /FVC | G/A                            | -0.050  | 0.009 | 3.09E-08 | -0.042  | 0.007 | 6.56E-09 | -0.045            | 0.006 | <b>1.40E-15</b> |
|                                 |                                                                  | FVC                   | G/A                            | -0.009  | 0.009 | 3.05E-01 | -0.026  | 0.007 | 3.07E-04 | -0.020            | 0.006 | 5.22E-04        |
| rs6441207<br>(chr3:158282459)   | <i>AK097794</i> (ncRNA_intronic)                                 | FEV <sub>1</sub>      | C/T                            | 0.029   | 0.008 | 2.07E-04 | 0.033   | 0.006 | 1.34E-07 | 0.031             | 0.005 | <b>1.23E-10</b> |
|                                 |                                                                  | FEV <sub>1</sub> /FVC | C/T                            | -0.003  | 0.008 | 6.56E-01 | 0.001   | 0.006 | 8.13E-01 | 0.000             | 0.005 | 9.25E-01        |
|                                 |                                                                  | FVC                   | C/T                            | 0.036   | 0.008 | 4.54E-06 | 0.036   | 0.006 | 5.85E-09 | 0.036             | 0.005 | <b>1.27E-13</b> |
| rs6856422<br>(chr4:106841962)   | <i>NPNT</i> (intronic)                                           | FEV <sub>1</sub>      | G/T                            | -0.045  | 0.008 | 6.22E-08 | -0.037  | 0.006 | 1.26E-08 | -0.040            | 0.005 | <b>5.60E-15</b> |
|                                 |                                                                  | FEV <sub>1</sub> /FVC | G/T                            | -0.044  | 0.008 | 1.30E-07 | -0.055  | 0.006 | 1.15E-17 | -0.051            | 0.005 | <b>1.51E-23</b> |
|                                 |                                                                  | FVC                   | G/T                            | -0.020  | 0.008 | 1.54E-02 | -0.019  | 0.006 | 3.97E-03 | -0.019            | 0.005 | 1.70E-04        |
| rs148274477<br>(chr6:142838173) | <i>GPR126</i> (dist=70770), <i>LOC153910</i> (dist=9419)         | FEV <sub>1</sub>      | C/T                            | 0.010   | 0.027 | 7.07E-01 | -0.057  | 0.019 | 2.42E-03 | -0.035            | 0.015 | 2.26E-02        |
|                                 |                                                                  | FEV <sub>1</sub> /FVC | C/T                            | -0.161  | 0.027 | 2.68E-09 | -0.162  | 0.019 | 5.63E-18 | -0.162            | 0.015 | <b>9.58E-26</b> |
|                                 |                                                                  | FVC                   | C/T                            | 0.114   | 0.027 | 3.07E-05 | 0.017   | 0.019 | 3.56E-01 | 0.048             | 0.015 | 1.77E-03        |
| rs34886460<br>(chr9:119359372)  | <i>ASTN2</i> (intronic)                                          | FEV <sub>1</sub>      | T/TA                           | 0.023   | 0.008 | 2.85E-03 | 0.015   | 0.006 | 1.13E-02 | 0.018             | 0.005 | 1.21E-04        |
|                                 |                                                                  | FEV <sub>1</sub> /FVC | T/TA                           | 0.041   | 0.008 | 6.75E-08 | 0.025   | 0.006 | 4.07E-05 | 0.031             | 0.005 | <b>4.72E-11</b> |
|                                 |                                                                  | FVC                   | T/TA                           | 0.000   | 0.008 | 9.72E-01 | 0.007   | 0.006 | 2.33E-01 | 0.004             | 0.005 | 3.62E-01        |
| rs2274116<br>(chr9:139094805)   | <i>LHX3</i> (exonic)                                             | FEV <sub>1</sub>      | C/T                            | 0.029   | 0.009 | 6.27E-04 | 0.029   | 0.007 | 1.09E-05 | 0.029             | 0.005 | <b>2.53E-08</b> |
|                                 |                                                                  | FEV <sub>1</sub> /FVC | C/T                            | -0.013  | 0.009 | 1.29E-01 | 0.001   | 0.007 | 9.00E-01 | -0.004            | 0.005 | 4.13E-01        |
|                                 |                                                                  | FVC                   | C/T                            | 0.041   | 0.009 | 2.68E-06 | 0.038   | 0.007 | 4.20E-09 | 0.039             | 0.005 | <b>5.55E-14</b> |
| rs11383346<br>(chr12:28283187)  | <i>PTHLH</i> (dist=158271), <i>CCDC91</i> (dist=126946)          | FEV <sub>1</sub>      | A/AT                           | -0.039  | 0.008 | 3.41E-07 | -0.034  | 0.006 | 5.37E-08 | -0.036            | 0.005 | <b>1.07E-13</b> |
|                                 |                                                                  | FEV <sub>1</sub> /FVC | A/AT                           | -0.002  | 0.008 | 8.38E-01 | -0.004  | 0.006 | 5.31E-01 | -0.003            | 0.005 | 5.37E-01        |
|                                 |                                                                  | FVC                   | A/AT                           | -0.043  | 0.008 | 3.83E-08 | -0.041  | 0.006 | 4.42E-11 | -0.042            | 0.005 | <b>9.52E-18</b> |
| rs10850377<br>(chr12:115201436) | <i>TBX3</i> (dist=79467), <i>MED13L</i> (dist=1194945)           | FEV <sub>1</sub>      | G/A                            | -0.047  | 0.008 | 6.68E-09 | -0.028  | 0.006 | 1.55E-05 | -0.035            | 0.005 | <b>2.50E-12</b> |
|                                 |                                                                  | FEV <sub>1</sub> /FVC | G/A                            | -0.020  | 0.008 | 1.10E-02 | -0.010  | 0.006 | 1.38E-01 | -0.014            | 0.005 | 6.00E-03        |
|                                 |                                                                  | FVC                   | G/A                            | -0.033  | 0.008 | 3.60E-05 | -0.027  | 0.006 | 2.67E-05 | -0.030            | 0.005 | <b>4.59E-09</b> |

| rs number (chr: position)       | Gene (function)                      | Measure               | Coded allele/<br>Non coded allele | Stage 1 |       |          | Stage 2 |       |          | Stage 1 + stage 2 |       |                 |
|---------------------------------|--------------------------------------|-----------------------|-----------------------------------|---------|-------|----------|---------|-------|----------|-------------------|-------|-----------------|
|                                 |                                      |                       |                                   | Beta    | SE    | P        | Beta    | SE    | P        | Beta              | SE    | P               |
| rs7155279<br>(chr14:92485881)   | TRIP11 (intronic)                    | FEV <sub>1</sub>      | G/T                               | -0.041  | 0.008 | 1.39E-07 | -0.022  | 0.006 | 4.17E-04 | -0.030            | 0.005 | <b>1.41E-09</b> |
|                                 |                                      | FEV <sub>1</sub> /FVC | G/T                               | -0.023  | 0.008 | 3.49E-03 | -0.015  | 0.006 | 2.10E-02 | -0.018            | 0.005 | 2.83E-04        |
|                                 |                                      | FVC                   | G/T                               | -0.031  | 0.008 | 8.62E-05 | -0.020  | 0.006 | 1.50E-03 | -0.024            | 0.005 | 8.06E-07        |
| rs117068593<br>(chr14:93118229) | RIN3 (exonic)                        | FEV <sub>1</sub>      | C/T                               | -0.048  | 0.010 | 2.72E-06 | -0.027  | 0.008 | 5.68E-04 | -0.035            | 0.006 | <b>2.25E-08</b> |
|                                 |                                      | FEV <sub>1</sub> /FVC | C/T                               | 0.008   | 0.010 | 4.23E-01 | -0.018  | 0.008 | 2.10E-02 | -0.008            | 0.006 | 1.79E-01        |
|                                 |                                      | FVC                   | C/T                               | -0.054  | 0.010 | 1.74E-07 | -0.022  | 0.008 | 5.83E-03 | -0.033            | 0.006 | 8.10E-08        |
| rs12149828<br>(chr16:10706328)  | EMP2(dist=31789), TEK5(dist=15033)   | FEV <sub>1</sub>      | G/A                               | 0.037   | 0.010 | 3.38E-04 | 0.022   | 0.008 | 7.31E-03 | 0.028             | 0.007 | 1.45E-05        |
|                                 |                                      | FEV <sub>1</sub> /FVC | G/A                               | 0.049   | 0.010 | 3.16E-06 | 0.035   | 0.008 | 3.33E-05 | 0.040             | 0.007 | <b>7.65E-10</b> |
|                                 |                                      | FVC                   | G/A                               | 0.005   | 0.010 | 6.12E-01 | 0.007   | 0.008 | 3.96E-01 | 0.006             | 0.007 | 3.27E-01        |
| rs113473882<br>(chr19:41124155) | LTBP4 (intronic)                     | FEV <sub>1</sub>      | T/C                               | -0.029  | 0.033 | 3.78E-01 | -0.019  | 0.028 | 5.00E-01 | -0.023            | 0.021 | 2.78E-01        |
|                                 |                                      | FEV <sub>1</sub> /FVC | T/C                               | -0.174  | 0.033 | 1.48E-07 | -0.138  | 0.028 | 1.00E-06 | -0.153            | 0.021 | <b>9.95E-13</b> |
|                                 |                                      | FVC                   | T/C                               | 0.073   | 0.033 | 2.88E-02 | 0.046   | 0.028 | 1.05E-01 | 0.057             | 0.022 | 8.02E-03        |
| rs134041<br>(chr22:28056338)    | MIAT(dist=983898), MN1(dist=87927)   | FEV <sub>1</sub>      | T/C                               | -0.045  | 0.008 | 4.19E-09 | -0.018  | 0.006 | 4.19E-03 | -0.028            | 0.005 | <b>3.03E-09</b> |
|                                 |                                      | FEV <sub>1</sub> /FVC | T/C                               | -0.025  | 0.008 | 1.06E-03 | -0.016  | 0.006 | 1.11E-02 | -0.019            | 0.005 | 5.45E-05        |
|                                 |                                      | FVC                   | T/C                               | -0.031  | 0.008 | 5.44E-05 | -0.017  | 0.006 | 7.20E-03 | -0.022            | 0.005 | 3.69E-06        |
| rs7050036<br>(chrX:15964845)    | AP1S2(dist=91708), GRPR(dist=176579) | FEV <sub>1</sub>      | T/A                               | -0.014  | 0.007 | 4.41E-02 | -0.003  | 0.005 | 6.03E-01 | -0.007            | 0.004 | 1.06E-01        |
|                                 |                                      | FEV <sub>1</sub> /FVC | T/A                               | -0.041  | 0.007 | 4.37E-09 | -0.013  | 0.005 | 1.60E-02 | -0.023            | 0.004 | <b>4.14E-08</b> |
|                                 |                                      | FVC                   | T/A                               | 0.010   | 0.007 | 1.47E-01 | 0.005   | 0.005 | 3.36E-01 | 0.007             | 0.004 | 1.01E-01        |

### Supplementary Table 3 Functional characterization of novel lung function loci

#### a) eQTL results

Results from eQTL analyses in blood<sup>6</sup> and lung<sup>7-9</sup> (details in **Supplementary Methods**) are presented here for variants in 2Mb regions (sentinel +/- 1Mb) in LD ( $r^2 > 0.3$ ) with the sentinel variant for all the 16 new sentinel variants, which (i) met an FDR threshold of 10%, and (ii) had eQTL  $P < 5 \times 10^{-5}$ . For each probeset we ranked variants according to their correlation with the sentinel SNP (as measured by  $r^2$ ) first and to their eQTL  $P$  value second, and we only present results for the top ranked variant for each probeset. Datasets were queried both for *cis* and *trans* eQTLs, but no *trans* results were significant, therefore the table only presents *cis* results. “Effect on expression” indicates whether the “Effect allele” was associated with increased gene expression (“+”) or with decreased gene expression (“-“). In the lung eQTL analyses for the autosomal chromosomes results from three different studies were meta-analysed, as indicated by “Dataset” on the table, however for X chromosome analyses were undertaken separately for males and females in each study (details are given in the “Dataset” column). No blood eQTL results were available for the X chromosome. This table presents results for an additional SNP (rs4926386) next to the *ENSA* region. Chr., chromosome.

| Sentinel rs number (chr: position) | Proxy rs number (chr: position) | R <sup>2</sup> with sentinel | eQTL <i>P</i> | Probeset id      | Gene Symbol                              | Effect allele | Effect on expression | Tissue | Dataset       |
|------------------------------------|---------------------------------|------------------------------|---------------|------------------|------------------------------------------|---------------|----------------------|--------|---------------|
| rs4926386 (chr1:149886135)         | rs4926386 (chr1:149886135)      | 1.00                         | 7.72E-06      | 100138305_TGI_at | <i>ARNT</i>                              | C             | -                    | lung   | meta-analysed |
|                                    | rs3754047 (chr1:150039207)      | 0.60                         | 1.51E-13      | 3890500          | <i>MRPS21</i>                            | A             | -                    | blood  | -             |
|                                    | rs3738320 (chr1:149982626)      | 0.38                         | 7.57E-06      | 100309612_TGI_at | <i>SV2A</i>                              | A             | +                    | lung   | meta-analysed |
|                                    | rs4926399 (chr1:149924299)      | 0.35                         | 1.82E-05      | 100123438_TGI_at | <i>MTMR11</i>                            | C             | -                    | lung   | meta-analysed |
| rs6681426 (chr1:150586971)         | rs6681426 (chr1:150586971)      | 1.00                         | 2.10E-68      | 100138305_TGI_at | <i>ARNT</i>                              | A             | -                    | lung   | meta-analysed |
|                                    | rs6681426 (chr1:150586971)      | 1.00                         | 5.21E-15      | 100302368_TGI_at | <i>LASS2</i>                             | A             | -                    | lung   | meta-analysed |
|                                    | rs6681426 (chr1:150586971)      | 1.00                         | 1.44E-13      | 100135055_TGI_at | <i>HORMAD1</i>                           | A             | -                    | lung   | meta-analysed |
|                                    | rs6681426 (chr1:150586971)      | 1.00                         | 1.66E-12      | 100151271_TGI_at | <i>LASS2</i>                             | A             | -                    | lung   | meta-analysed |
|                                    | rs6681426 (chr1:150586971)      | 1.00                         | 1.85E-12      | 100309723_TGI_at | <i>ARNT</i>                              | A             | +                    | lung   | meta-analysed |
|                                    | rs6681426 (chr1:150586971)      | 1.00                         | 8.55E-11      | 100308717_TGI_at | <i>GOLPH3L</i>                           | A             | -                    | lung   | meta-analysed |
|                                    | rs6681426 (chr1:150586971)      | 1.00                         | 6.09E-10      | 100144443_TGI_at | cDNA clone that overlaps <i>ADAMTSL4</i> | A             | +                    | lung   | meta-analysed |
|                                    | rs6681426 (chr1:150586971)      | 1.00                         | 1.09E-07      | 100306322_TGI_at | <i>ARNT</i>                              | A             | +                    | lung   | meta-analysed |
|                                    | rs6681426 (chr1:150586971)      | 1.00                         | 8.75E-06      | 100307575_TGI_at | <i>MRPS21</i>                            | A             | +                    | lung   | meta-analysed |
|                                    | rs6681426 (chr1:150586971)      | 1.00                         | 1.49E-05      | 100313509_TGI_at | <i>FAM63A</i>                            | A             | +                    | lung   | meta-analysed |
|                                    | rs2280078 (chr1:150600181)      | 0.99                         | 1.08E-120     | 6330484          | <i>CTSS</i>                              | C             | +                    | blood  | -             |
|                                    | rs2280078 (chr1:150600181)      | 0.99                         | 1.13E-20      | 1430278          | <i>CTSK</i>                              | C             | +                    | blood  | -             |
|                                    | rs2280078 (chr1:150600181)      | 0.99                         | 1.94E-05      | 2190040          | <i>ARNT</i>                              | C             | -                    | blood  | -             |
|                                    | rs4970969 (chr1:150612361)      | 0.91                         | 1.58E-05      | 100310890_TGI_at | <i>ARNT</i>                              | T             | -                    | lung   | meta-analysed |
|                                    | rs11204718 (chr1:150709785)     | 0.84                         | 4.12E-08      | 100159164_TGI_at | <i>GOLPH3L</i>                           | C             | -                    | lung   | meta-analysed |
|                                    | rs11204718 (chr1:150709785)     | 0.84                         | 3.00E-07      | 100143466_TGI_at | <i>GOLPH3L</i>                           | C             | -                    | lung   | meta-analysed |
|                                    | rs7521898 (chr1:150707596)      | 0.80                         | 2.22E-19      | 3370121          | <i>LASS2</i>                             | A             | +                    | blood  | -             |
|                                    | rs7521898 (chr1:150707596)      | 0.80                         | 2.52E-17      | 6380154          | <i>LASS2</i>                             | A             | +                    | blood  | -             |

| Sentinel rs number (chr: position) | Proxy rs number (chr: position) | R <sup>2</sup> with sentinel | eQTL <i>P</i> | Probeset id      | Gene Symbol              | Effect allele | Effect on expression | Tissue | Dataset       |
|------------------------------------|---------------------------------|------------------------------|---------------|------------------|--------------------------|---------------|----------------------|--------|---------------|
|                                    | rs11204691 (chr1:150644339)     | 0.76                         | 4.27E-05      | 2640338          | <i>ARNT</i>              | T             | +                    | blood  | -             |
|                                    | rs878471 (chr1:150547747)       | 0.73                         | 4.55E-08      | 100144721_TGI_at | <i>RPRD2</i>             | G             | -                    | lung   | meta-analysed |
|                                    | rs878471 (chr1:150547747)       | 0.73                         | 6.87E-06      | 100161206_TGI_at | <i>ENSA</i>              | G             | -                    | lung   | meta-analysed |
|                                    | rs897815 (chr1:150879101)       | 0.64                         | 4.89E-11      | 4480192          | <i>CDC42SE1, C1orf56</i> | G             | -                    | blood  | -             |
|                                    | rs897815 (chr1:150879101)       | 0.64                         | 3.99E-07      | 4390372          | <i>BNIP1</i>             | G             | -                    | blood  | -             |
|                                    | rs897815 (chr1:150879101)       | 0.64                         | 5.60E-07      | 4540288          | <i>CDC42SE1, C1orf56</i> | G             | -                    | blood  | -             |
|                                    | rs3768013 (chr1:150815411)      | 0.63                         | 3.14E-05      | 6450722          | <i>SETDB1</i>            | A             | -                    | blood  | -             |
|                                    | rs11204693 (chr1:150647987)     | 0.55                         | 1.20E-05      | 7380100          | <i>MCL1</i>              | T             | -                    | blood  | -             |
|                                    | rs11204664 (chr1:150531380)     | 0.48                         | 2.47E-08      | 100156777_TGI_at | <i>MRPS21</i>            | C             | +                    | lung   | meta-analysed |
|                                    | rs11204664 (chr1:150531380)     | 0.48                         | 1.50E-06      | 100130530_TGI_at | <i>ECM1</i>              | C             | +                    | lung   | meta-analysed |
|                                    | rs2305814 (chr1:150958977)      | 0.45                         | 2.99E-05      | 4280162          | <i>SCNM1</i>             | C             | -                    | blood  | -             |
|                                    | rs486836 (chr1:150875967)       | 0.40                         | 1.78E-05      | 100125530_TGI_at | <i>CTSS</i>              | A             | +                    | lung   | meta-analysed |
| rs201204531 (chr1:219963090)       | rs1338230 (chr1:219963090)      | 0.31                         | 1.27E-06      | 100159938_TGI_at | <i>SLC30A10</i>          | G             | +                    | lung   | meta-analysed |
| rs6441207 (chr3:158282459)         | rs6441207 (chr3:158282459)      | 1.00                         | 2.30E-08      | 100301782_TGI_at | <i>MLF1</i>              | C             | -                    | lung   | meta-analysed |
|                                    | rs6441207 (chr3:158282459)      | 1.00                         | 3.21E-06      | 100304858_TGI_at | <i>MLF1</i>              | C             | -                    | lung   | meta-analysed |
|                                    | rs112353818 (chr3:158239479)    | 0.82                         | 2.63E-09      | 100150755_TGI_at | <i>GFM1</i>              | G             | +                    | lung   | meta-analysed |
|                                    | rs112353818 (chr3:158239479)    | 0.82                         | 2.90E-06      | 100123606_TGI_at | <i>MLF1</i>              | G             | -                    | lung   | meta-analysed |
|                                    | rs7620927 (chr3:158245883)      | 0.81                         | 1.22E-05      | 3440195          | <i>GFM1</i>              | G             | +                    | blood  | -             |
|                                    | rs12492884 (chr3:158252566)     | 0.53                         | 2.62E-06      | 60670            | <i>GFM1, LXN</i>         | G             | -                    | blood  | -             |
|                                    | rs1656377 (chr3:158285280)      | 0.50                         | 2.32E-06      | 100312821_TGI_at | <i>MLF1</i>              | C             | +                    | lung   | meta-analysed |
|                                    | rs2731122 (chr3:158295280)      | 0.37                         | 2.62E-06      | 100141104_TGI_at | <i>GFM1</i>              | G             | -                    | lung   | meta-analysed |
|                                    | rs63740961 (chr3:158295171)     | 0.31                         | 8.55E-06      | 100301664_TGI_at | <i>GFM1</i>              | C             | -                    | lung   | meta-analysed |

| Sentinel rs number (chr: position) | Proxy rs number (chr: position) | R <sup>2</sup> with sentinel | eQTL <i>P</i> | Probeset id      | Gene Symbol                           | Effect allele | Effect on expression | Tissue | Dataset       |
|------------------------------------|---------------------------------|------------------------------|---------------|------------------|---------------------------------------|---------------|----------------------|--------|---------------|
| rs6856422 (chr4:106841962)         | rs4600917 (chr4:106829645)      | 0.77                         | 2.89E-06      | 4860553          | <i>INTS12</i>                         | C             | -                    | blood  | -             |
|                                    | rs2553449 (chr4:106698892)      | 0.42                         | 3.17E-05      | 5360487          | <i>GSTCD</i>                          | T             | +                    | blood  | -             |
| rs34886460 (chr9:119359372)        | rs1372335 (chr9:119403743)      | 0.62                         | 1.10E-06      | 5670088          | <i>TRIM32</i>                         | T             | +                    | blood  | -             |
| rs2274116 (chr9:139094805)         | rs2274116 (chr9:139094805)      | 1.00                         | 1.81E-06      | 100124395_TGI_at | <i>QSOX2</i>                          | C             | +                    | lung   | meta-analysed |
|                                    | rs10858246 (chr9:139102831)     | 0.88                         | 4.78E-08      | 3830605          | <i>C9orf151</i>                       | C             | +                    | blood  | -             |
|                                    | rs3780190 (chr9:139099073)      | 0.43                         | 1.32E-05      | 3060494          | <i>CARD9</i>                          | G             | -                    | blood  | -             |
| rs11383346 (chr12:28283187)        | rs11383346 (chr12:28283187)     | 1.00                         | 1.73E-13      | 100137632_TGI_at | <i>cDNA clone that maps to CCDC91</i> | NA            | -                    | lung   | meta-analysed |
|                                    | rs11049391 (chr12:28322273)     | 0.90                         | 1.55E-05      | 100124630_TGI_at | <i>CCDC91</i>                         | G             | +                    | lung   | meta-analysed |
|                                    | rs10843114 (chr12:28303296)     | 0.35                         | 6.29E-06      | 100133373_TGI_at | <i>CCDC91</i>                         | C             | -                    | lung   | meta-analysed |
| rs7155279 (chr14:92485881)         | rs7155279 (chr14:92485881)      | 1.00                         | 1.01E-10      | 100132576_TGI_at | <i>ATXN3</i>                          | G             | -                    | lung   | meta-analysed |
|                                    | rs7155279 (chr14:92485881)      | 1.00                         | 3.38E-06      | 100160661_TGI_at | <i>TRIP11</i>                         | G             | -                    | lung   | meta-analysed |
|                                    | rs76497846 (chr14:92531888)     | 0.99                         | 1.80E-05      | 100127017_TGI_at | <i>CPSF2</i>                          | G             | -                    | lung   | meta-analysed |
|                                    | rs7157056 (chr14:92498033)      | 0.94                         | 3.00E-34      | 4670441          | <i>FBLN5</i>                          | G             | +                    | blood  | -             |
|                                    | rs7157056 (chr14:92498033)      | 0.94                         | 1.23E-29      | 5690639          | <i>FBLN5</i>                          | G             | +                    | blood  | -             |
|                                    | rs7157056 (chr14:92498033)      | 0.94                         | 1.12E-19      | 2760136          | <i>TRIP11</i>                         | G             | +                    | blood  | -             |
|                                    | rs10151561 (chr14:92430184)     | 0.75                         | 2.05E-06      | 100300526_TGI_at | <i>ATXN3</i>                          | A             | -                    | lung   | meta-analysed |
|                                    | rs10129429 (chr14:92430831)     | 0.75                         | 1.72E-05      | 100143127_TGI_at | <i>NDUFB1</i>                         | G             | +                    | lung   | meta-analysed |
|                                    | rs7145052 (chr14:92461192)      | 0.69                         | 3.35E-05      | 5090037          | <i>NDUFB1</i>                         | T             | -                    | blood  | -             |
|                                    | rs111269625 (chr14:92514370)    | 0.56                         | 2.50E-13      | 100148617_TGI_at | <i>ATXN3</i>                          | G             | +                    | lung   | meta-analysed |
|                                    | rs111269625 (chr14:92514370)    | 0.56                         | 1.13E-08      | 100306579_TGI_at | <i>ATXN3</i>                          | G             | +                    | lung   | meta-analysed |
|                                    | rs111269625 (chr14:92514370)    | 0.56                         | 1.60E-05      | 100137755_TGI_at | <i>ATXN3</i>                          | G             | -                    | lung   | meta-analysed |

| Sentinel rs number (chr: position) | Proxy rs number (chr: position) | R <sup>2</sup> with sentinel | eQTL <i>P</i> | Probeset id      | Gene Symbol  | Effect allele | Effect on expression | Tissue | Dataset        |
|------------------------------------|---------------------------------|------------------------------|---------------|------------------|--------------|---------------|----------------------|--------|----------------|
| rs12149828 (chr16:10706328)        | rs8053116 (chr16:10719601)      | 0.55                         | 5.51E-06      | 100123005_TGI_at | <i>EMP2</i>  | A             | +                    | lung   | meta-analysed  |
| rs113473882 (chr19:41124155)       | rs113434779 (chr19:41236459)    | 0.49                         | 1.15E-05      | 100302701_TGI_at | <i>NUMBL</i> | C             | -                    | lung   | meta-analysed  |
| rs7050036 (chrX:15964845)          | rs798183 (chrX:15840426)        | 0.62                         | 1.96E-08      | 100302651_TGI_at | <i>ZRSR2</i> | T             | +                    | lung   | UBC_male       |
|                                    | rs798183 (chrX:15840426)        | 0.62                         | 3.18E-07      | 100302651_TGI_at | <i>ZRSR2</i> | T             | +                    | lung   | Laval_male     |
|                                    | rs798183 (chrX:15840426)        | 0.62                         | 1.34E-06      | 100302651_TGI_at | <i>ZRSR2</i> | T             | +                    | lung   | Groningen_male |
|                                    | rs798183 (chrX:15840426)        | 0.62                         | 7.79E-06      | 100302651_TGI_at | <i>ZRSR2</i> | T             | +                    | lung   | UBC_female     |
|                                    | rs798157 (chrX:15810140)        | 0.53                         | 2.99E-09      | 100311509_TGI_at | <i>AP1S2</i> | T             | +                    | lung   | Laval_male     |
|                                    | rs798157 (chrX:15810140)        | 0.53                         | 5.49E-08      | 100122762_TGI_at | <i>AP1S2</i> | T             | +                    | lung   | Laval_male     |

## b) DNase hypersensitivity sites

DNase hypersensitivity sites as defined by ENCODE<sup>10</sup>, which contain at least one variant strongly correlated ( $r^2 > 0.8$ ) with any of the new 16 sentinel variants are presented here. The “Signal Value” is a measurement of average enrichment in the region and the “Score value” is a normalized value that ranges from 0 to 1,000 based on the signal value<sup>10,11</sup>. Only DNase hypersensitivity sites with “Score value” > 100 are presented. Cell type abbreviations are: A549, epithelial cell line derived from a lung carcinoma tissue; AG04450, fetal lung fibroblast; HMVEC-LBI, blood microvascular endothelial cells, lung-derived; HMVEC-LLy, lymphatic microvascular endothelial cells, lung-derived; HPF, pulmonary fibroblasts isolated from lung tissue; HPAEC, pulmonary artery endothelial cells; HPAF, pulmonary artery fibroblasts; NHLF, lung fibroblasts; WI-38, embryonic lung fibroblast cells, hTERT immortalized, includes Raf1 construct. Chr., chromosome.

| Sentinel rs number (chr: position) | Proxy rs number (chr: position) | R <sup>2</sup> with sentinel | Cell type | Chr. | Start     | End       | Score value | Signal value |
|------------------------------------|---------------------------------|------------------------------|-----------|------|-----------|-----------|-------------|--------------|
| rs6681426 (chr1:150586971)         | rs6655975 (chr1:150542128)      | 0.97                         | HPAEC     | 1    | 150542080 | 150542230 | 102         | 15           |
| rs6681426 (chr1:150586971)         | rs6655975 (chr1:150542128)      | 0.97                         | HPAEC     | 1    | 150542080 | 150542230 | 102         | 15           |
| rs201204531 (chr1:219963090)       | rs10863500 (chr1:219961690)     | 1.00                         | AG04450   | 1    | 219961560 | 219961710 | 101         | 24           |
| rs2274116 (chr9:119359372)         | rs4836757 (chr9:119326613)      | 0.98                         | A549      | 9    | 119326565 | 119326715 | 100         | 21           |
| rs11383346 (chr12:28283187)        | rs2881788 (chr12:28272574)      | 0.82                         | WI-38     | 12   | 28272520  | 28272670  | 100         | 10           |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28283780)      | 0.99                         | AG04450   | 12   | 28283700  | 28283850  | 106         | 173          |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28283780)      | 0.99                         | HPAF      | 12   | 28283700  | 28283850  | 129         | 1340         |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28283780)      | 0.99                         | HPAEC     | 12   | 28283720  | 28283870  | 137         | 272          |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28283780)      | 0.99                         | HMVEC-LLy | 12   | 28283740  | 28283890  | 110         | 739          |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28283780)      | 0.99                         | HPF       | 12   | 28283740  | 28283890  | 115         | 253          |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28283780)      | 0.99                         | WI-38     | 12   | 28283740  | 28283890  | 116         | 297          |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28283780)      | 0.99                         | NHLF      | 12   | 28283740  | 28283890  | 121         | 948          |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28283780)      | 0.99                         | A549      | 12   | 28283760  | 28283910  | 100         | 21           |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28283780)      | 0.99                         | HMVEC-LBI | 12   | 28283760  | 28283910  | 182         | 1082         |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28285003)      | 0.99                         | HMVEC-LBI | 12   | 28285000  | 28285150  | 101         | 16           |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28406157)      | 0.82                         | HPAF      | 12   | 28406080  | 28406230  | 100         | 19           |
| rs11383346 (chr12:28283187)        | rs7310453 (chr12:28406157)      | 0.82                         | NHLF      | 12   | 28406080  | 28406230  | 102         | 84           |
| rs10850377 (chr12:115201436)       | rs78649052 (chr12:115200597)    | 0.97                         | HPAF      | 12   | 115200500 | 115200650 | 102         | 77           |
| rs10850377 (chr12:115201436)       | rs78649052 (chr12:115200597)    | 0.97                         | AG04450   | 12   | 115200500 | 115200650 | 103         | 81           |
| rs10850377 (chr12:115201436)       | rs78649052 (chr12:115200597)    | 0.97                         | HPF       | 12   | 115200500 | 115200650 | 109         | 148          |
| rs10850377 (chr12:115201436)       | rs78649052 (chr12:115200597)    | 0.97                         | WI-38     | 12   | 115200500 | 115200650 | 109         | 172          |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | AG04450   | 14   | 93070260  | 93070410  | 103         | 74           |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | AG04450   | 14   | 93070260  | 93070410  | 103         | 74           |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | WI-38     | 14   | 93070260  | 93070410  | 103         | 57           |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | WI-38     | 14   | 93070260  | 93070410  | 103         | 57           |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | AG04450   | 14   | 93070260  | 93070410  | 103         | 74           |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | AG04450   | 14   | 93070260  | 93070410  | 103         | 74           |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | WI-38     | 14   | 93070260  | 93070410  | 103         | 57           |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | WI-38     | 14   | 93070260  | 93070410  | 103         | 57           |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | HPAF      | 14   | 93070260  | 93070410  | 104         | 164          |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | HPAF      | 14   | 93070260  | 93070410  | 104         | 164          |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | HPF       | 14   | 93070260  | 93070410  | 104         | 66           |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | HPF       | 14   | 93070260  | 93070410  | 104         | 66           |
| rs117068593 (chr14:93118229)       | rs78440108 (chr14:93070286)     | 0.90                         | NHLF      | 14   | 93070260  | 93070410  | 104         | 191          |



| Sentinel rs number (chr: position) | Proxy rs number (chr: position) | R <sup>2</sup> with sentinel | Cell type | Chr. | Start    | End      | Score value | Signal value |
|------------------------------------|---------------------------------|------------------------------|-----------|------|----------|----------|-------------|--------------|
| rs117068593 (chr14:93118229)       | rs72697299 (chr14:93070367)     | 0.90                         | HPAEC     | 14   | 93070280 | 93070430 | 103         | 21           |
| rs117068593 (chr14:93118229)       | rs72697299 (chr14:93070367)     | 0.90                         | HMVEC-LLy | 14   | 93070300 | 93070450 | 100         | 19           |
| rs117068593 (chr14:93118229)       | rs72697299 (chr14:93070367)     | 0.90                         | HMVEC-LLy | 14   | 93070300 | 93070450 | 100         | 19           |
| rs117068593 (chr14:93118229)       | rs72697299 (chr14:93070367)     | 0.90                         | HMVEC-LLy | 14   | 93070300 | 93070450 | 100         | 19           |
| rs117068593 (chr14:93118229)       | rs72697299 (chr14:93070367)     | 0.90                         | HMVEC-LLy | 14   | 93070300 | 93070450 | 100         | 19           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | WI-38     | 14   | 93103660 | 93103810 | 102         | 44           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | WI-38     | 14   | 93103660 | 93103810 | 102         | 44           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | WI-38     | 14   | 93103660 | 93103810 | 102         | 44           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | WI-38     | 14   | 93103660 | 93103810 | 102         | 44           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | HPF       | 14   | 93103660 | 93103810 | 103         | 48           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | HPF       | 14   | 93103660 | 93103810 | 103         | 48           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | HPF       | 14   | 93103660 | 93103810 | 103         | 48           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | HPF       | 14   | 93103660 | 93103810 | 103         | 48           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | AG04450   | 14   | 93103680 | 93103830 | 101         | 29           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | AG04450   | 14   | 93103680 | 93103830 | 101         | 29           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | AG04450   | 14   | 93103680 | 93103830 | 101         | 29           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | AG04450   | 14   | 93103680 | 93103830 | 101         | 29           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | HPAF      | 14   | 93103720 | 93103870 | 100         | 23           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | HPAF      | 14   | 93103720 | 93103870 | 100         | 23           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | HPAF      | 14   | 93103720 | 93103870 | 100         | 23           |
| rs117068593 (chr14:93118229)       | rs7143806 (chr14:93103729)      | 0.94                         | HPAF      | 14   | 93103720 | 93103870 | 100         | 23           |
| rs117068593 (chr14:93118229)       | rs201493181 (chr14:93112309)    | 0.99                         | HPAF      | 14   | 93112300 | 93112450 | 102         | 85           |
| rs117068593 (chr14:93118229)       | rs201493181 (chr14:93112309)    | 0.99                         | HPAF      | 14   | 93112300 | 93112450 | 102         | 85           |
| rs117068593 (chr14:93118229)       | rs201493181 (chr14:93112309)    | 0.99                         | HPAF      | 14   | 93112300 | 93112450 | 102         | 85           |
| rs117068593 (chr14:93118229)       | rs201493181 (chr14:93112309)    | 0.99                         | HPAF      | 14   | 93112300 | 93112450 | 102         | 85           |
| rs12149828 (chr16:10706328)        | rs12596425 (chr16:10713425)     | 0.95                         | NHLF      | 16   | 10713420 | 10713570 | 100         | 12           |
| rs134041 (chr22:28056338)          | rs134077 (chr22:28063227)       | 0.97                         | HPAF      | 22   | 28063120 | 28063270 | 101         | 64           |
| rs134041 (chr22:28056338)          | rs134117 (chr22:28082715)       | 0.86                         | HPAEC     | 22   | 28082620 | 28082770 | 106         | 47           |
| rs134041 (chr22:28056338)          | rs134117 (chr22:28082715)       | 0.86                         | HMVEC-LLy | 22   | 28082640 | 28082790 | 100         | 21           |
| rs134041 (chr22:28056338)          | rs134117 (chr22:28082715)       | 0.86                         | AG04450   | 22   | 28082640 | 28082790 | 101         | 28           |
| rs134041 (chr22:28056338)          | rs134117 (chr22:28082715)       | 0.86                         | HPF       | 22   | 28082640 | 28082790 | 103         | 59           |
| rs134041 (chr22:28056338)          | rs134117 (chr22:28082715)       | 0.86                         | WI-38     | 22   | 28082640 | 28082790 | 103         | 57           |
| rs134041 (chr22:28056338)          | rs134117 (chr22:28082715)       | 0.86                         | NHLF      | 22   | 28082640 | 28082790 | 104         | 190          |
| rs134041 (chr22:28056338)          | rs134117 (chr22:28082715)       | 0.86                         | HPAF      | 22   | 28082640 | 28082790 | 109         | 411          |

| Sentinel rs number (chr: position) | Proxy rs number (chr: position) | R <sup>2</sup> with sentinel | Cell type | Chr. | Start    | End      | Score value | Signal value |
|------------------------------------|---------------------------------|------------------------------|-----------|------|----------|----------|-------------|--------------|
| rs134041 (chr22:28056338)          | rs134117 (chr22:28082715)       | 0.86                         | HMVEC-LBI | 22   | 28082640 | 28082790 | 117         | 228          |
| rs134041 (chr22:28056338)          | rs134117 (chr22:28082715)       | 0.86                         | A549      | 22   | 28082680 | 28082830 | 100         | 45           |

### c) Human Protein Atlas results

Protein expression results in the respiratory system for epithelial cells, pneumocytes and macrophages for a subset of genes for each of the regions that contain the 16 sentinel variants (see gene selection criteria in **Supplementary Methods**) were assessed in the Human Protein Atlas<sup>12</sup> and are presented here. If no results were available in the Human Protein Atlas a hyphen (“-”) is presented on the table. Chr., chromosome; H, high; M, medium; L, low; ND not detected.

| rs number (chr: position)    | Measure          | Gene Symbol | Respiratory epithelial cells, Nasopharynx (antibody1 staining, antibody2 staining, annotated protein expression) | Respiratory epithelial cells, Bronchus (antibody1 staining, antibody2 staining, annotated protein expression) | Pneumocytes, lung (antibody1 staining, antibody2 staining, annotated protein expression) | Macrophages, lung (antibody1 staining, antibody2 staining, annotated protein expression) |
|------------------------------|------------------|-------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| rs6681426 (chr1:150586971)   | FEV <sub>1</sub> | ARNT        | M,M,M                                                                                                            | M,L,L                                                                                                         | M,M,M                                                                                    | M,M,M                                                                                    |
| rs6681426 (chr1:150586971)   | FEV <sub>1</sub> | CTSS        | M,L,M                                                                                                            | M,M,M                                                                                                         | ND,ND,ND                                                                                 | H,H,H                                                                                    |
| rs6681426 (chr1:150586971)   | FEV <sub>1</sub> | LASS2       | L,-,-                                                                                                            | M,-,-                                                                                                         | H,-,-                                                                                    | ND,-,-                                                                                   |
| rs201204531 (chr1:219963090) | FF               | SLC30A10    | ND,-,-                                                                                                           | ND,-,-                                                                                                        | L,-,-                                                                                    | M,-,-                                                                                    |
| rs61067109 (chr2:18292452)   | FF               | KCNS3       | M,-,-                                                                                                            | -,-,-                                                                                                         | L,-,-                                                                                    | M,-,-                                                                                    |
| rs6441207 (chr3:158282459)   | FVC              | GFM1        | M,-,-                                                                                                            | H,-,-                                                                                                         | ND,-,-                                                                                   | H,-,-                                                                                    |
| rs6441207 (chr3:158282459)   | FVC              | MLF1        | H,-,-                                                                                                            | M,-,-                                                                                                         | ND,-,-                                                                                   | H,-,-                                                                                    |
| rs6856422 (chr4:106841962)   | FF               | NPNT        | ND,-,-                                                                                                           | ND,-,-                                                                                                        | H,-,-                                                                                    | ND,-,-                                                                                   |
| rs6856422 (chr4:106841962)   | FF               | INTS12      | H,-,-                                                                                                            | M,-,-                                                                                                         | M,-,-                                                                                    | M,-,-                                                                                    |
| rs6856422 (chr4:106841962)   | FF               | GSTCD       | M,-,-                                                                                                            | M,-,-                                                                                                         | ND,-,-                                                                                   | M,-,-                                                                                    |
| rs148274477 (chr6:142838173) | FF               | GPR126      | ND,-,-                                                                                                           | ND,-,-                                                                                                        | ND,-,-                                                                                   | ND,-,-                                                                                   |
| rs34886460 (chr9:119359372)  | FF               | TRIM32      | M,-,-                                                                                                            | M,-,-                                                                                                         | ND,-,-                                                                                   | ND,-,-                                                                                   |
| rs2274116 (chr9:139094805)   | FVC              | QSOX2       | M,-,-                                                                                                            | H,-,-                                                                                                         | ND,-,-                                                                                   | L,-,-                                                                                    |
| rs11383346 (chr12:28283187)  | FVC              | CCDC91      | H,-,-                                                                                                            | H,-,-                                                                                                         | M,-,-                                                                                    | M,-,-                                                                                    |
| rs10850377 (chr12:115201436) | FEV <sub>1</sub> | TBX3        | L,-,-                                                                                                            | L,-,-                                                                                                         | ND,-,-                                                                                   | H,-,-                                                                                    |
| rs7155279 (chr14:92485881)   | FEV <sub>1</sub> | TRIP11      | H,-,-                                                                                                            | H,-,-                                                                                                         | H,-,-                                                                                    | H,-,-                                                                                    |
| rs7155279 (chr14:92485881)   | FEV <sub>1</sub> | ATXN3       | M,H,H                                                                                                            | ND,H,H                                                                                                        | ND,H,H                                                                                   | ND,H,H                                                                                   |
| rs117068593 (chr14:93118229) | FEV <sub>1</sub> | RIN3        | -,-,-                                                                                                            | ND,-,-                                                                                                        | ND,-,-                                                                                   | M,-,-                                                                                    |
| rs12149828 (chr16:10706328)  | FF               | EMP2        | ND,-,-                                                                                                           | M,-,-                                                                                                         | M,-,-                                                                                    | M,-,-                                                                                    |
| rs113473882 (chr19:41124155) | FF               | LTBP4       | M,-,-                                                                                                            | -,-,-                                                                                                         | M,-,-                                                                                    | M,-,-                                                                                    |
| rs134041 (chr22:28056338)    | FEV <sub>1</sub> | MN1         | H,-,-                                                                                                            | H,-,-                                                                                                         | H,-,-                                                                                    | ND,-,-                                                                                   |
| rs7050036 (chrX:15964845)    | FF               | ZRSR2       | L,-,-                                                                                                            | M,-,-                                                                                                         | M,-,-                                                                                    | M,-,-                                                                                    |
| rs7050036 (chrX:15964845)    | FF               | AP1S2       | ND,-,-                                                                                                           | L,-,-                                                                                                         | ND,-,-                                                                                   | ND,-,-                                                                                   |

#### d) Differential gene expression in fetal lung

Publicly available gene expression data from fetal lung samples spanning pseudoglandular and canalicular stages of lung development<sup>13</sup> were queried for a subset of genes for each of the regions that contain the 16 sentinel variants (see criteria in the **Supplementary Methods**). Adj.  $P < 0.05$  are highlighted in bold, and genes with all the probes showing an effect on the same direction and with at least 33% of the probes with adjusted  $P < 0.05$  are also highlighted in bold. Chr., chromosome, Probe id, Affymetrix probe id; Average expression, average expression for probe during the entire time period (genes with Average expression values  $> 8$  can be considered highly expressed); Adj.  $P$ , adjusted  $P$  (Benjamini & Hochberg method<sup>14</sup>) for differential expression over time; Beta, mean change in gene expression per day during the studied period (7-22 weeks of gestational age); chr., chromosome.

| rs number (chr: position)    | Probe id    | Gene Symbol | Average expression | Adj. P          | Beta   |
|------------------------------|-------------|-------------|--------------------|-----------------|--------|
| rs6681426 (chr1:150586971)   | 233724_at   | <b>ARNT</b> | 4.55               | <b>4.58E-03</b> | 0.009  |
| rs6681426 (chr1:150586971)   | 230619_at   | <b>ARNT</b> | 7.55               | <b>6.32E-03</b> | 0.012  |
| rs6681426 (chr1:150586971)   | 210828_s_at | <b>ARNT</b> | 5.03               | 3.13E-01        | 0.003  |
| rs6681426 (chr1:150586971)   | 218222_x_at | <b>ARNT</b> | 6.82               | 3.52E-01        | 0.002  |
| rs6681426 (chr1:150586971)   | 218221_at   | <b>ARNT</b> | 8.11               | 5.17E-01        | 0.002  |
| rs6681426 (chr1:150586971)   | 231016_s_at | <b>ARNT</b> | 7.36               | 9.51E-01        | 0.000  |
| rs6681426 (chr1:150586971)   | 232617_at   | <b>CTSS</b> | 6.17               | <b>3.02E-04</b> | 0.015  |
| rs6681426 (chr1:150586971)   | 202901_x_at | <b>CTSS</b> | 3.59               | <b>5.90E-03</b> | 0.010  |
| rs6681426 (chr1:150586971)   | 202902_s_at | <b>CTSS</b> | 6.06               | 1.20E-01        | 0.007  |
| rs6681426 (chr1:150586971)   | 222212_s_at | LASS2       | 9.61               | 1.97E-01        | 0.003  |
| rs201204531 (chr1:219963090) | 220435_at   | SLC30A10    | 3.42               | 2.56E-01        | 0.002  |
| rs61067109 (chr2:18292452)   | 205968_at   | KCNS3       | 7.98               | 9.79E-01        | 0.000  |
| rs6441207 (chr3:158282459)   | 232296_s_at | GFM1        | 7.02               | <b>1.10E-02</b> | -0.008 |
| rs6441207 (chr3:158282459)   | 225158_at   | GFM1        | 7.73               | <b>2.39E-02</b> | -0.008 |
| rs6441207 (chr3:158282459)   | 225161_at   | GFM1        | 7.76               | <b>4.34E-02</b> | -0.006 |
| rs6441207 (chr3:158282459)   | 232295_at   | GFM1        | 3.57               | 1.94E-01        | -0.002 |
| rs6441207 (chr3:158282459)   | 225153_at   | GFM1        | 9.50               | 6.64E-01        | 0.001  |
| rs6441207 (chr3:158282459)   | 220903_at   | GFM1        | 3.81               | 8.44E-01        | 0.000  |
| rs6441207 (chr3:158282459)   | 204783_at   | <b>MLF1</b> | 7.23               | <b>1.42E-02</b> | 0.010  |
| rs6441207 (chr3:158282459)   | 204784_s_at | <b>MLF1</b> | 8.41               | 9.07E-01        | 0.001  |
| rs6856422 (chr4:106841962)   | 235387_at   | GSTCD       | 6.32               | <b>8.55E-04</b> | -0.012 |
| rs6856422 (chr4:106841962)   | 1554518_at  | GSTCD       | 5.80               | <b>1.50E-02</b> | -0.005 |
| rs6856422 (chr4:106841962)   | 220063_at   | GSTCD       | 5.61               | 8.62E-02        | -0.004 |
| rs6856422 (chr4:106841962)   | 241126_at   | GSTCD       | 3.46               | 4.88E-01        | 0.001  |
| rs6856422 (chr4:106841962)   | 218616_at   | INTS12      | 8.22               | 2.10E-01        | -0.004 |
| rs6856422 (chr4:106841962)   | 225911_at   | NPNT        | 9.01               | <b>6.65E-06</b> | 0.011  |
| rs6856422 (chr4:106841962)   | 244747_at   | NPNT        | 4.36               | 9.75E-01        | 0.000  |
| rs148274477 (chr6:142838173) | 1553025_at  | GPR126      | 3.77               | <b>1.69E-02</b> | 0.004  |
| rs148274477 (chr6:142838173) | 213094_at   | GPR126      | 9.73               | 1.98E-01        | -0.003 |
| rs148274477 (chr6:142838173) | 233887_at   | GPR126      | 7.66               | 9.87E-01        | 0.000  |
| rs34886460 (chr9:119359372)  | 236233_at   | TRIM32      | 4.75               | 4.48E-01        | 0.002  |
| rs34886460 (chr9:119359372)  | 203846_at   | TRIM32      | 8.21               | 5.55E-01        | 0.001  |
| rs2274116 (chr9:139094805)   | 235239_at   | QSOX2       | 5.35               | 6.01E-02        | -0.003 |
| rs2274116 (chr9:139094805)   | 227146_at   | QSOX2       | 7.05               | 1.34E-01        | -0.003 |
| rs11383346 (chr12:28283187)  | 218545_at   | CCDC91      | 7.08               | 6.76E-01        | 0.002  |
| rs11383346 (chr12:28283187)  | 1570571_at  | CCDC91      | 4.55               | 8.94E-01        | 0.001  |
| rs10850377 (chr12:115201436) | 219682_s_at | TBX3        | 8.67               | <b>9.91E-03</b> | 0.006  |
| rs10850377 (chr12:115201436) | 225544_at   | TBX3        | 9.56               | 2.70E-01        | 0.002  |
| rs10850377 (chr12:115201436) | 222917_s_at | TBX3        | 5.83               | 4.56E-01        | 0.002  |
| rs10850377 (chr12:115201436) | 229576_s_at | TBX3        | 7.36               | 5.21E-01        | 0.002  |
| rs10850377 (chr12:115201436) | 229565_x_at | TBX3        | 4.41               | 6.14E-01        | 0.001  |
| rs10850377 (chr12:115201436) | 228344_s_at | TBX3        | 4.41               | 7.96E-01        | -0.001 |
| rs10850377 (chr12:115201436) | 243234_at   | TBX3        | 3.63               | 9.83E-01        | 0.000  |
| rs7155279 (chr14:92485881)   | 216657_at   | ATXN3       | 3.89               | <b>9.97E-04</b> | 0.006  |
| rs7155279 (chr14:92485881)   | 217321_x_at | ATXN3       | 3.38               | 1.00E-01        | 0.002  |
| rs7155279 (chr14:92485881)   | 238723_at   | ATXN3       | 6.46               | 1.89E-01        | 0.007  |

| rs number (chr: position)    | Probe id    | Gene Symbol  | Average expression | Adj. P          | Beta   |
|------------------------------|-------------|--------------|--------------------|-----------------|--------|
| rs7155279 (chr14:92485881)   | 205416_s_at | ATXN3        | 5.48               | 4.77E-01        | -0.002 |
| rs7155279 (chr14:92485881)   | 235240_at   | ATXN3        | 6.87               | 6.96E-01        | -0.001 |
| rs7155279 (chr14:92485881)   | 205415_s_at | ATXN3        | 6.50               | 9.51E-01        | 0.000  |
| rs7155279 (chr14:92485881)   | 233182_x_at | ATXN3        | 5.27               | 9.59E-01        | 0.000  |
| rs7155279 (chr14:92485881)   | 230211_at   | TRIP11       | 4.74               | 3.53E-01        | 0.003  |
| rs7155279 (chr14:92485881)   | 210760_x_at | TRIP11       | 4.62               | 6.02E-01        | 0.001  |
| rs7155279 (chr14:92485881)   | 236160_at   | TRIP11       | 6.77               | 6.46E-01        | -0.001 |
| rs7155279 (chr14:92485881)   | 209778_at   | TRIP11       | 5.61               | 6.75E-01        | 0.002  |
| rs117068593 (chr14:93118229) | 1562005_at  | RIN3         | 4.13               | 5.05E-02        | 0.004  |
| rs117068593 (chr14:93118229) | 60471_at    | RIN3         | 7.46               | 2.57E-01        | 0.002  |
| rs117068593 (chr14:93118229) | 220439_at   | RIN3         | 4.30               | 4.91E-01        | -0.001 |
| rs117068593 (chr14:93118229) | 219457_s_at | RIN3         | 5.94               | 7.43E-01        | -0.001 |
| rs117068593 (chr14:93118229) | 219456_s_at | RIN3         | 5.00               | 7.92E-01        | 0.001  |
| rs12149828 (chr16:10706328)  | 204975_at   | <b>EMP2</b>  | 8.29               | <b>3.68E-06</b> | 0.014  |
| rs12149828 (chr16:10706328)  | 225078_at   | <b>EMP2</b>  | 9.08               | <b>1.42E-05</b> | 0.011  |
| rs12149828 (chr16:10706328)  | 225079_at   | <b>EMP2</b>  | 8.71               | <b>8.62E-05</b> | 0.010  |
| rs12149828 (chr16:10706328)  | 238500_at   | <b>EMP2</b>  | 4.73               | 9.78E-02        | 0.004  |
| rs113473882 (chr19:41124155) | 227989_at   | LTBP4        | 4.68               | 1.30E-01        | -0.003 |
| rs113473882 (chr19:41124155) | 204442_x_at | LTBP4        | 8.44               | 3.89E-01        | 0.004  |
| rs113473882 (chr19:41124155) | 213176_s_at | LTBP4        | 8.03               | 9.31E-01        | 0.001  |
| rs113473882 (chr19:41124155) | 210628_x_at | LTBP4        | 6.83               | 9.96E-01        | 0.000  |
| rs134041 (chr22:28056338)    | 205330_at   | MN1          | 5.44               | 1.60E-01        | -0.005 |
| rs7050036 (chrX:15964845)    | 228415_at   | <b>AP1S2</b> | 7.82               | <b>9.12E-05</b> | -0.009 |
| rs7050036 (chrX:15964845)    | 230264_s_at | <b>AP1S2</b> | 9.67               | <b>3.97E-02</b> | -0.004 |
| rs7050036 (chrX:15964845)    | 203300_x_at | <b>AP1S2</b> | 9.07               | 1.52E-01        | -0.004 |
| rs7050036 (chrX:15964845)    | 203299_s_at | <b>AP1S2</b> | 7.55               | 6.26E-01        | -0.001 |
| rs7050036 (chrX:15964845)    | 208174_x_at | ZRSR2        | 6.99               | 4.29E-01        | 0.002  |
| rs7050036 (chrX:15964845)    | 213876_x_at | ZRSR2        | 7.18               | 5.82E-01        | 0.001  |

### e) Differential gene expression in COPD vs. non COPD ever smoker samples

Publicly available gene expression data from bronchial brushings of individuals with COPD and of ever smoking individuals without COPD<sup>15</sup> were queried for a subset of genes for each of the regions that contain the 16 sentinel variants (see criteria in **Supplementary Methods**) are presented. There was no probe available for *ZRSR2* in this analysis. Adj.  $P < 0.05$  are highlighted in bold. “Probe id”, affymetrix probe id; Adj.P,  $P$  value after adjustment for multiple testing using the Benjamini & Hochberg method<sup>14</sup>; FC, fold change between cases and controls ( $>1$  up regulated in cases); chr., chromosome.

| rs number (chr: position)    | Probe id  | Gene Symbol | Adj. P          | FC   |
|------------------------------|-----------|-------------|-----------------|------|
| rs6681426 (chr1:150586971)   | 405_at    | ARNT        | 8.53E-02        | 1.04 |
| rs6681426 (chr1:150586971)   | 1520_at   | CTSS        | 1.04E-01        | 1.06 |
| rs6681426 (chr1:150586971)   | 29956_at  | LASS2       | 5.78E-01        | 1.02 |
| rs201204531 (chr1:219963090) | 55532_at  | SLC30A10    | 9.35E-01        | 1.00 |
| rs61067109 (chr2:18292452)   | 3790_at   | KCNS3       | 9.23E-01        | 0.99 |
| rs6441207 (chr3:158282459)   | 85476_at  | GFM1        | 7.28E-01        | 0.99 |
| rs6441207 (chr3:158282459)   | 4291_at   | MLF1        | <b>1.74E-03</b> | 1.12 |
| rs6856422 (chr4:106841962)   | 79807_at  | GSTCD       | 3.84E-01        | 1.03 |
| rs6856422 (chr4:106841962)   | 57117_at  | INTS12      | 2.57E-01        | 1.04 |
| rs6856422 (chr4:106841962)   | 255743_at | NPNT        | 7.90E-02        | 1.10 |
| rs148274477 (chr6:142838173) | 57211_at  | GPR126      | 2.86E-01        | 1.07 |
| rs34886460 (chr9:119359372)  | 22954_at  | TRIM32      | 8.29E-01        | 1.01 |
| rs2274116 (chr9:139094805)   | 169714_at | QSOX2       | 3.22E-01        | 0.97 |
| rs11383346 (chr12:28283187)  | 55297_at  | CCDC91      | 1.26E-01        | 1.05 |
| rs10850377 (chr12:115201436) | 6926_at   | TBX3        | 5.43E-01        | 0.97 |
| rs7155279 (chr14:92485881)   | 4287_at   | ATXN3       | <b>2.07E-02</b> | 1.07 |
| rs7155279 (chr14:92485881)   | 9321_at   | TRIP11      | 5.72E-01        | 1.03 |
| rs117068593 (chr14:93118229) | 79890_at  | RIN3        | 1.65E-01        | 0.96 |
| rs12149828 (chr16:10706328)  | 2013_at   | EMP2        | 9.84E-01        | 1.00 |
| rs113473882 (chr19:41124155) | 8425_at   | LTBP4       | 1.18E-01        | 0.95 |
| rs134041 (chr22:28056338)    | 4330_at   | MN1         | 8.36E-01        | 0.99 |
| rs7050036 (chrX:15964845)    | 8905_at   | AP1S2       | 6.61E-01        | 1.02 |
| rs7050036 (chrX:15964845)    | NA        | ZRSR2       | NA              | NA   |

## f) Sentinel and functional variants annotation and joint analysis results

Annotations were provided using ENSEMBL's Variant Effect Predictor<sup>16</sup>. Functional variants were defined as variants within 1 Mb of the sentinel variant, which were annotated as 'deleterious' by SIFT<sup>17</sup>, 'probably damaging' or 'potentially damaging' by PolyPhen-2<sup>18</sup>, had a CADD<sup>19</sup> scaled score  $\geq 20$ , or had a GWAVA score  $> 0.5$ , and were in linkage disequilibrium (LD) with the sentinel variant ( $r^2 > 0.3$ ) and/or had nominal evidence of association ( $P < 5 \times 10^{-4}$ ) (see **Supplementary Methods**). Only functional variants, which explained the association of the sentinel variant (sentinel variant joint  $P > 0.01$ ), are listed. *RIN3* locus, where the sentinel variant is a missense variant, is also presented. Stage 1 unconditional analysis results and joint analysis results are shown in alternating white and grey colours. Conditional analyses were undertaken using GCTA<sup>20</sup> and LD information was estimated using UK BiLEVE data (details in the **Supplementary Methods**). GCTA did not produce joint results for rs34093919 and rs113473882, since they are almost in perfect LD. Chr., chromosome; freq., frequency.

| rs number (chr: position)    | Variant type | Function                                | Gene Symbol    | SIFT               | PolyPhen                  | GWAVA score | CADD scaled score | Measure               | R <sup>2</sup> with sentinel | MAF  | Unconditional results |       |          | Joint analysis |       |          |
|------------------------------|--------------|-----------------------------------------|----------------|--------------------|---------------------------|-------------|-------------------|-----------------------|------------------------------|------|-----------------------|-------|----------|----------------|-------|----------|
|                              |              |                                         |                |                    |                           |             |                   |                       |                              |      | Beta                  | SE    | P        | Beta           | SE    | P        |
| rs6681426 (chr1:150586971)   | sentinel     | Intron variant                          | ENSA           | -                  | -                         | 0.21        | 0.93              | FEV <sub>1</sub>      | 1.00                         | 0.36 | 0.042                 | 0.008 | 1.07E-07 | 0.034          | 0.014 | 1.23E-02 |
| rs9803935 (chr1:150552622)   | functional   | Upstream gene variant                   | MCL1           | -                  | -                         | 0.51        | 7.67              | FEV <sub>1</sub>      | 0.68                         | 0.48 | 0.036                 | 0.008 | 2.14E-06 | 0.009          | 0.013 | 4.83E-01 |
| rs6681426 (chr1:150586971)   | sentinel     | Intron variant                          | ENSA           | -                  | -                         | 0.21        | 0.93              | FEV <sub>1</sub>      | 1.00                         | 0.36 | 0.042                 | 0.008 | 1.07E-07 | 0.032          | 0.014 | 2.02E-02 |
| rs1053732 (chr1:150597890)   | functional   | Intron variant                          | ENSA           | -                  | -                         | 0.55        | 3.88              | FEV <sub>1</sub>      | 0.68                         | 0.48 | 0.037                 | 0.008 | 1.20E-06 | 0.011          | 0.013 | 3.93E-01 |
| rs6441207 (chr3:158282459)   | sentinel     | Intron variant, nc transcript variant   | AK097794       | -                  | -                         | 0.1         | 0.68              | FVC                   | 1.00                         | 0.41 | 0.036                 | 0.008 | 4.54E-06 | 0.030          | 0.014 | 3.76E-02 |
| rs939117 (chr3:158200869)    | functional   | Intron variant                          | RSRC1          | -                  | -                         | 0.6         | 16.60             | FVC                   | 0.73                         | 0.47 | 0.031                 | 0.008 | 3.89E-05 | 0.007          | 0.014 | 6.29E-01 |
| rs148274477 (chr6:142838173) | sentinel     | Intergenic variant                      | -              | -                  | -                         | 0.04        | 12.33             | FEV <sub>1</sub> /FVC | 1.00                         | 0.02 | -0.161                | 0.027 | 2.68E-09 | -0.095         | 0.056 | 8.98E-02 |
| rs17280293 (chr6:142688969)  | functional   | Missense variant                        | GPR126         | Deleterious (0)    | Possibly damaging (0.602) | -           | 21.90             | FEV <sub>1</sub> /FVC | 0.85                         | 0.02 | -0.154                | 0.026 | 4.72E-09 | -0.073         | 0.055 | 1.82E-01 |
| rs12149828 (chr16:10706328)  | sentinel     | Intergenic variant                      | -              | -                  | -                         | 0.21        | 1.06              | FEV <sub>1</sub> /FVC | 1.00                         | 0.17 | 0.049                 | 0.010 | 3.16E-06 | 0.048          | 0.021 | 1.88E-02 |
| rs12448455 (chr16:10711678)  | functional   | Intergenic variant                      | -              | -                  | -                         | 0.6         | 3.84              | FEV <sub>1</sub> /FVC | 0.80                         | 0.19 | 0.039                 | 0.010 | 5.74E-05 | 0.000          | 0.019 | 9.86E-01 |
| rs113473882 (chr19:41124155) | sentinel     | Intron variant                          | LTBP4          | -                  | -                         | 0.11        | 2.46              | FEV <sub>1</sub> /FVC | 1.00                         | 0.02 | -0.174                | 0.033 | 1.48E-07 | NA             | NA    | NA       |
| rs34093919 (chr19:41117300)  | functional   | Missense variant, splice region variant | LTBP4          | Deleterious (0.05) | Possibly damaging (0.841) | -           | 18.35             | FEV <sub>1</sub> /FVC | 0.99                         | 0.02 | -0.163                | 0.032 | 4.82E-07 | NA             | NA    | NA       |
| rs134041 (chr22:28056338)    | sentinel     | Intergenic variant                      | -              | -                  | -                         | 0.46        | 19.28             | FEV <sub>1</sub>      | 1.00                         | 0.43 | -0.045                | 0.008 | 4.19E-09 | -0.036         | 0.016 | 2.63E-02 |
| rs134117 (chr22:28082715)    | functional   | Intron variant, nc transcript variant   | RP1-213J1P_B.1 | -                  | -                         | 0.6         | 12.58             | FEV <sub>1</sub>      | 0.78                         | 0.41 | -0.042                | 0.008 | 4.43E-08 | -0.010         | 0.016 | 5.51E-01 |
| rs117068593 (chr4:93118229)  | sentinel     | Missense variant                        | RIN3           | Tolerated (0.07)   | Unknown (0)               | -           | 14.37             | FEV <sub>1</sub>      | 1                            | 0.18 | -0.048                | 0.010 | 2.72E-06 | NA             | NA    | NA       |

**Supplementary Table 4** Literature search results for genes overlapping or proximal to novel lung function sentinel SNP and genes which contain a SNP with  $r^2 > 0.3$  with lead SNP

A systematic literature search was performed for each gene. Three main websites were used. Firstly, each 'gene name' was searched for in Gene Cards ([www.genecards.org](http://www.genecards.org)), as well as the International Mouse Phenotyping Consortium database ([www.mousephenotype.org](http://www.mousephenotype.org)). Secondly, each 'gene name', 'gene name' and 'lung', 'gene name' and 'lung disease', and 'gene name' and 'development' were searched for in Pubmed ([www.pubmed.com](http://www.pubmed.com)). Information regarding gene function, association to human disease and animal model phenotyping was identified. Genes included in the gene column include genes containing SNP with  $r^2 > 0.3$  with sentinel SNP or genes selected as priority genes for each region (see criteria in **Supplementary Methods**). Chr., chromosome..

| rs number (chr: position:variant type, function) | Genes containing SNPs with $r^2 > 0.3$ with sentinel variant or implicated through eQTL analyses                                                  | Description of genes in region and biological plausibility                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Animal model with lung function or pulmonary phenotype                                                                                                                                        |
|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| rs6681426<br>(1:150586971:SNP, intergenic)       | ADAMTSL4;ADAMTSL4-AS1;ANXA9;ARNT;CELS3;CTSK;CTSS;CYCSP51;ENSA;GOLPH3L;HORMAD1;LINC00568;MCL1;RN7SL473P;RP11-235D19.2;RP11-363I22.3;SETDB1;SNORA40 | <p><b>ADAMTSL4:</b> Member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs)-like gene family. Associated diseases include eye disorders such as ectopia lentis<sup>21</sup>.</p> <p><b>ADAMTSL4-AS1:</b> ADAMTSL4 antisense RNA 1.</p> <p><b>ANXA9:</b> Annexins are calcium-dependent phospholipid-binding proteins. Has calcium-binding sites which are required for annexins to aggregate and cooperatively bind anionic phospholipids and extracellular matrix proteins.</p> <p><b>ARNT:</b> Binds to ligand-bound aryl hydrocarbon receptor. Aids the movement of a complex to the nucleus, where it promotes the expression of genes involved in xenobiotic metabolism. Also a co-factor for transcriptional regulation by hypoxia-inducible factor 1 which is important in lung development<sup>22</sup>. Chromosomal translocation ARNT with ETV6 gene on chromosome 12 has been described in leukaemia<sup>23</sup>.</p> <p><b>CERS2 (LASS2):</b> Also known as LASS2. Involved in sphingolipid synthesis<sup>24</sup>. Associated with Breast Cancer<sup>25</sup>.</p> <p><b>CTSK:</b> Lysosomal cysteine proteinase involved in bone remodeling and resorption<sup>26</sup>. Mutations in this gene are the cause of pycnodysostosis<sup>27</sup>.</p> <p><b>CTSS:</b> Lysosomal cysteine proteinase which is involved in the degradation of antigenic proteins to peptides for presentation on MHC class II molecules<sup>28</sup>. Associated diseases include Atherosclerosis, Lung Fibrosis and defects in the immune system<sup>29</sup>.</p> <p><b>CYCSP51:</b> Cytochrome C, Somatic Pseudogene 51.</p> <p><b>ENSA:</b> Inhibits sulfonylurea binding to beta-cell membranes, reduces cloned K(ATP) channel currents, and stimulates insulin secretion from beta-cells, therefore is a candidate gene involved in Diabetes<sup>30</sup>.</p> <p><b>GOLPH3L:</b> Potential regulatory role in Golgi trafficking<sup>31</sup>. Associated with Rhabdomyosarcoma<sup>32</sup>.</p> <p><b>HORMAD1:</b> May play a role in the progression of meiosis and is a potential marker for cancer<sup>33</sup>.</p> <p><b>LINC00568:</b> Long Intergenic Non-Protein Coding RNA 568.</p> <p><b>MCL1:</b> Regulates apoptosis<sup>34</sup>. Mutations found in Leukemia<sup>35</sup>.</p> <p><b>RN7SL473P:</b> RNA, 7SL, Cytoplasmic 473, Pseudogene.</p> <p><b>SETDB1:</b> Histone methyltransferase which regulates histone methylation, gene silencing, transcriptional repression and is associated with Huntington's disease<sup>36</sup>.</p> <p><b>SNORA40:</b> Small nucleolar RNA40.</p> | <p><b>CERS2 (LASS2):</b> null mice show lung inflammation and airway obstruction<sup>37</sup>.</p> <p><b>CTSK:</b> null mice develop more lung fibrosis than wild type mice<sup>38</sup>.</p> |
| rs201204531<br>(1:219963090:INDEL, intergenic)   | AC096643.1;RNA5SP76;SLC30A10                                                                                                                      | <p><b>RNA5SP76:</b> RNA, 5S Ribosomal Pseudogene 76, no data available.</p> <p><b>SLC30A10:</b> Protein critical in maintaining manganese levels with loss of function mutations resulting in dystonia, adult-onset parkinsonism and chronic liver disease<sup>39</sup>.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                               |
| rs61067109<br>(2:18292452:SNP, intergenic)       | KCNS3                                                                                                                                             | <p><b>KCNS3:</b> Regulates the resting membrane potential and SNP's in this gene are associated with airway hyper-responsiveness<sup>40</sup>. Associated with migraine<sup>41</sup>.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                               |

| rs number (chr: position:variant type, function) | Genes containing SNPs with $r^2 > 0.3$ with sentinel variant or implicated through eQTL analyses                                           | Description of genes in region and biological plausibility                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Animal model with lung function or pulmonary phenotype                                                                                   |
|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| rs6441207<br>(3:158282459:SNP, ncRNA_intronic)   | <i>GFM1</i> ; <i>MLF1</i> ; <i>MTAPP1</i> ; <i>RARR ES1</i> ; <i>AK097794</i> ( <i>RP11-538P18.2</i> ); <i>RP11-79M21.3</i> ; <i>RSRC1</i> | <b>GFM1</b> : Mitochondrial GTPase that catalyzes the GTP-dependent ribosomal translocation step during translation elongation <sup>42</sup> . Diseases associated with GFM1 include combined oxidative phosphorylation deficiency 1 <sup>43</sup> .<br><b>MLF1</b> : Involved in lineage commitment of primary haemopoietic progenitors by restricting erythroid formation and enhancing myeloid formation <sup>44</sup> . Mutations involved in myelodysplastic syndromes and myeloid leukemia <sup>45</sup> . Binds DNA and affects the expression of a number of genes so may function as a transcription factor in the nucleus <sup>46</sup> .<br><b>MTAPP1</b> : methylthioadenosine phosphorylase pseudogene 1.<br><b>RARR ES1</b> : Retinoid acid (RA) receptor-responsive gene which inhibits the cytoplasmic carboxypeptidase AGBL2 and may regulate the alpha-tubulin tyrosination cycle <sup>47</sup> . Associated with Ovarian Endometriosis and downregulated in prostate cancer <sup>48</sup> .<br><b>RSRC1</b> : Encodes a serine and arginine rich-related protein involved in mRNA splicing. Associated with height <sup>49</sup> and Schizophrenia <sup>50</sup> . |                                                                                                                                          |
| rs6856422<br>(4:106841962:SNP, intronic)         | <i>GSTCD</i> ; <i>INTS12</i> ; <i>NPNT</i>                                                                                                 | <b>GSTCD</b> : Has homology with the glutathione S-transferase (GST) super family of enzymes <sup>51</sup> . May be involved in the detoxification of products of oxidative stress and synthesis of steroid hormones <sup>52</sup> . However, GSTCD lacks key functional domains important for GST activity. <i>GSTCD</i> expression in human lung tissue is ubiquitous <sup>9</sup> .<br><b>INTS12</b> : Subunit of the Integrator complex, which associates with the C-terminal domain of RNA polymerase II large subunit and mediates 3' end processing of small nuclear RNAs <sup>53</sup> . <i>INTS12</i> expression in human lung is found predominantly in epithelial cells and pneumocytes <sup>9</sup> .<br><b>NPNT</b> : Potentially involved in the development of many tissues <sup>54</sup> . Associated with include acute and chronic hepatitis <sup>55</sup> .                                                                                                                                                                                                                                                                                                        |                                                                                                                                          |
| rs148274477<br>(6:142838173:SNP, intergenic)     | <i>GPR126</i> ; <i>LOC153910</i> ( <i>RP11-440G9.1</i> )                                                                                   | <b>GPR126</b> : Encodes a G protein-coupled receptor, with variations affecting stature <sup>49,56-58</sup> , birth length <sup>59</sup> , and adolescent idiopathic scoliosis <sup>60</sup> . May be required for normal differentiation of promyelinating Schwann cells and for normal myelination of axons <sup>61</sup> . It is expressed in adult mice lung <sup>62</sup> . It is required for mice embryonic viability and cardiovascular development <sup>63</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                          |
| rs34886460<br>(9:119359372:INDEL, intronic)      | <i>TRIM32</i>                                                                                                                              | <b>ASTN2</b> : Expressed in the brain and may function in neuronal migration. Associated with migraine <sup>64</sup> .<br><b>TRIM32</b> : Protein interacts with the activation domain of the HIV-1 Tat protein. Associated with Bardet-Biedl syndrome (a ciliopathic disorder) <sup>65</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                          |
| rs2274116<br>(9:139094805:SNP, exonic)           | <i>LHX3</i> ; <i>QSOX2</i>                                                                                                                 | <b>LHX3</b> : Carries the LIM domain, a unique cysteine-rich zinc-binding domain. Transcription factor required for pituitary development and motor neuron specification. Mutations cause combined pituitary hormone deficiency 3 <sup>66</sup> .<br><b>QSOX2</b> : May contribute to disulfide bond formation in a variety of secreted proteins. Regulates the sensitization of neuroblastoma cells for IFN-gamma-induced cell death <sup>67</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                          |
| rs11383346<br>(12:28283187:INDEL, intergenic)    | <i>CCDC91</i> ; <i>RP11-874G11.1</i> ; <i>RP11-967K21.1</i> ; <i>RP11-967K21.2</i>                                                         | <b>CCDC91</b> : Associated with brain white matter structure and development <sup>68</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                          |
| rs10850377<br>(12:115201436:SNP, intergenic)     | <i>RP4-601P9.1</i> ; <i>RP4-601P9.2</i> ; <i>TBX3</i>                                                                                      | <b>TBX3</b> : Encodes a transcription factor involved in the regulation of developmental processes in limbs and genitals <sup>69</sup> . Mutations cause ulnar-mammary and Holt-Oram syndromes <sup>70</sup> . It is involved in the TGFβ1 signaling pathway <sup>71,72</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                          |
| rs7155279<br>(14:92485881:SNP, intronic)         | <i>ATXN3</i> ; <i>FBLN5</i> ; <i>RP11-529H20.6</i> ; <i>TRIP11</i>                                                                         | <b>ATXN3</b> : Deubiquitinating enzyme involved in protein homeostasis maintenance, transcription, cytoskeleton regulation, myogenesis and degradation of misfolded chaperone substrates. Associated with Machado-Joseph disease (spinocerebellar ataxia-3) <sup>73</sup> .<br><b>FBLN5</b> : Encodes a secreted, extracellular matrix protein. Promotes adhesion of endothelial cells through interaction of integrins and the RGD motif <sup>74</sup> . Defects in gene cause Cutis Laxa, autosomal recessive, type ia, and Hereditary Sensorimotor Neuropathy with Hyperelastic Skin <sup>75</sup> . Involved in tissue repair in COPD <sup>76</sup> and elastogenesis and lung                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>FBLN5</b> : Homozygous mutant mice have expanded lungs containing dilated alveoli (most severe in peripheral regions) <sup>80</sup> . |

| rs number (chr: position:variant type, function) | Genes containing SNPs with $r^2 > 0.3$ with sentinel variant or implicated through eQTL analyses                  | Description of genes in region and biological plausibility                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Animal model with lung function or pulmonary phenotype                                                                                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                  |                                                                                                                   | development <sup>77</sup> .<br><b>TRIP11</b> : Protein is associated with the Golgi apparatus <sup>78</sup> . Mutations in this gene cause achondrogenesis type IA (most severe form of dwarfism bone/cartilage malformations) <sup>79</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Adult <i>fibulin-5</i> <sup>-/-</sup> mice have disruptions in the alveolar structure and disruption to distal airways was found in P3 neonates <sup>81</sup> .                                                                                                                                                                                                                                                                                                   |
| rs117068593 (14:93118229:SNP, exonic)            | <i>RIN3</i>                                                                                                       | <b>RIN3</b> : Member of the RIN family of Ras interaction-interference protein <sup>82</sup> . Associated with Paget's disease <sup>83</sup> , COPD <sup>84</sup> and Alzheimer's disease <sup>85</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| rs12149828 (16:10706328:SNP, intergenic)         | <i>EMP2</i> ; <i>TEKT5</i>                                                                                        | <b>EMP2</b> : Involved in molecular interactions during implantation <sup>86</sup> . Diseases associated include charcot-marie-tooth disease type 1 <sup>87</sup> .<br><b>TEKT5</b> : Tektins are structural components of ciliary and flagellar microtubules. TEKT5 is implicated in sperm motility in mice <sup>88</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| rs113473882 (19:41124155:SNP, intronic)          | <i>CTC-490E21.12</i> ; <i>CYP2B6</i> ; <i>CYP2B7P</i> ; <i>ITPKC</i> ; <i>LTBP4</i> ; <i>NUMBL</i> ; <i>RAB4B</i> | <b>CYP2B6 and CYP2B7P</b> : Cytochrome P450 proteins are monooxygenases which are involved in drug metabolism and synthesis of cholesterol, steroids and lipids. Enzymes are involved in an NADPH-dependent electron transport pathway.<br><b>ITPKC</b> : Encodes inositol 1,4,5-trisphosphate (Ins(1,4,5)P(3)) 3-kinase enzymes. Has nuclear import and export activity. Associated with Kawasaki disease <sup>89</sup> .<br><b>LTBP4</b> : Binds transforming growth factor beta (TGFB) as it is secreted and targeted to the extracellular matrix. COPD risk associated gene with deregulated expression in the basal cells of smokers <sup>90</sup> .<br><b>NUMBL</b> : Has a role in neurogenesis <sup>91</sup> .<br><b>RAB4B</b> : RAB proteins are members of the RAS superfamily of small GTPases that are involved in vesicular trafficking <sup>92</sup> .                                                                                                                                  | <b>LTBP4</b> : Mice deficient in Latent TGFβ Binding Protein 4 (Ltbp4) display a defect in lung septation and elastogenesis <sup>77</sup> . Mice with <i>LTBP4</i> disruption show a pulmonary emphysema-like condition at birth which increases in severity with age. The lungs of <i>LTBP4</i> -disrupted mice had less alveolar spaces and those present were enlarged and inflated. Mice also developed cardiomyopathy and colorectal cancers <sup>93</sup> . |
| rs134041(22:28056338:SNP, intergenic)            | <i>MN1</i> ; <i>RP1-213J1P__B.1</i> ; <i>RP11-375H17.1</i>                                                        | <b>MN1</b> : Translocation of MN1 is associated with Leukemia <sup>94</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| rs7050036(X:15964845:SNP, intergenic)            | <i>AP1S2</i> ; <i>GRPR</i> ; <i>RNU5F-7P</i> ; <i>SETP15</i> ; <i>ZRSR2</i>                                       | <b>AP1S2</b> : Adaptor protein complex 1 subunit 2 found at the cytoplasmic face of coated vesicles in the Golgi complex. Mediates the recruitment of clathrin and the recognition of sorting signals within transmembrane receptors. Associated diseases include dandy-walker malformation with mental retardation <sup>95,96</sup> , and basal ganglia disease <sup>97</sup> .<br><b>GRPR</b> : Receptor for Gastrin-releasing peptide which regulates gastrointestinal and central nervous system functions including smooth muscle cell contraction and epithelial cell proliferation. Expressed by pulmonary neuroendocrine cells and known to stimulate growth and maturation of lung development <sup>98,99</sup> .<br><b>RNU5F-7P</b> : RNA, U5F Small Nuclear 7, Pseudogene.<br><b>SETP15</b> : SET Pseudogene 15.<br><b>ZRSR2</b> : Zinc Finger with RNA-Binding Motif which encodes an essential splicing factor which associates with U2 snRNA. Linked to myelodysplasia <sup>100</sup> . |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

### **Supplementary Table 5** Associations of top signals with other traits

Associations with lung function in children (a)), separately in ever and never smokers (b)), with smoking behaviour (c)) and with other traits as in the GWAS catalog<sup>101</sup> (d)).

#### **a) Effect of top hits on children**

Stage 2 results, as well as results in 5,062,506 children (8-9 years of age) in ALSPAC<sup>102</sup> are presented for the new 16 sentinel variants. *P* values that meet a Bonferroni correction for 16 tests ( $P < 3.13 \times 10^{-3}$ ) in ALSPAC are highlighted in bold. Chr., chromosome; dist., distance; Freq., frequency; N., effective sample size; Imp., imputation.

| rs number<br>(chr:position)     | Gene Symbol (function)                                              | Measure               | Coded<br>allele | Other<br>allele | Stage 2                  |        |       |          | ALSPAC                   |                |        |       |                 |
|---------------------------------|---------------------------------------------------------------------|-----------------------|-----------------|-----------------|--------------------------|--------|-------|----------|--------------------------|----------------|--------|-------|-----------------|
|                                 |                                                                     |                       |                 |                 | Coded<br>allele<br>freq. | Beta   | SE    | P        | Coded<br>allele<br>freq. | Imp<br>quality | Beta   | SE    | P               |
| rs6681426<br>(chr1:150586971)   | <i>MCL1</i> (dist=34757),<br><i>ENSA</i> (dist=7628)                | FEV <sub>1</sub>      | G               | A               | 0.35                     | 0.021  | 0.006 | 1.11E-03 | 0.35                     | 0.99           | 0.046  | 0.030 | 1.25E-01        |
| rs201204531<br>(chr1:219963090) | <i>LYPLAL1</i> (dist=576883),<br><i>RNU5F-1</i> (dist=83529)        | FEV <sub>1</sub> /FVC | A               | ATG             | 0.38                     | -0.027 | 0.006 | 1.76E-05 | 0.38                     | 0.97           | -0.048 | 0.029 | 9.79E-02        |
| rs61067109<br>(chr2:18292452)   | <i>KCNS3</i> (dist=178227),<br><i>NT5C1B-RDH14</i><br>(dist=443537) | FEV <sub>1</sub> /FVC | G               | A               | 0.77                     | -0.042 | 0.007 | 6.61E-09 | 0.76                     | 1.00           | -0.043 | 0.033 | 1.93E-01        |
| rs6441207<br>(chr3:158282459)   | <i>RP11-538P18.2</i><br>(ncRNA_intronic)                            | FVC                   | C               | T               | 0.59                     | 0.036  | 0.006 | 5.70E-09 | 0.59                     | 0.98           | 0.118  | 0.029 | <b>4.72E-05</b> |
| rs6856422<br>(chr4:106841962)   | <i>NPNT</i> (intronic)                                              | FEV <sub>1</sub> /FVC | G               | T               | 0.56                     | -0.055 | 0.006 | 1.13E-17 | 0.55                     | 0.86           | -0.074 | 0.030 | 1.36E-02        |
| rs148274477<br>(chr6:142838173) | <i>GPR126</i> (dist=70770),<br><i>RP11-440G9.1</i><br>(dist=9419)   | FEV <sub>1</sub> /FVC | C               | T               | 0.97                     | -0.162 | 0.019 | 5.66E-18 | 0.97                     | 0.76           | -0.165 | 0.094 | 7.92E-02        |
| rs34886460<br>(chr9:119359372)  | <i>ASTN2</i> (intronic)                                             | FEV <sub>1</sub> /FVC | T               | TA              | 0.54                     | 0.025  | 0.006 | 4.09E-05 | 0.54                     | 0.98           | -0.019 | 0.028 | 4.97E-01        |
| rs2274116<br>(chr9:139094805)   | <i>LHX3</i> (exonic)                                                | FVC                   | C               | T               | 0.66                     | 0.038  | 0.007 | 4.16E-09 | 0.68                     | 0.84           | 0.060  | 0.033 | 6.90E-02        |
| rs11383346<br>(chr12:28283187)  | <i>PTHLH</i> (dist=158271),<br><i>CCDC91</i> (dist=126946)          | FVC                   | A               | AT              | 0.41                     | -0.041 | 0.006 | 4.29E-11 | 0.42                     | 0.97           | -0.014 | 0.029 | 6.29E-01        |
| rs10850377<br>(chr12:115201436) | <i>TBX3</i> (dist=79467),<br><i>MED13L</i> (dist=1194945)           | FEV <sub>1</sub>      | G               | A               | 0.65                     | -0.028 | 0.006 | 1.50E-05 | 0.65                     | 0.96           | -0.031 | 0.031 | 3.17E-01        |
| rs7155279<br>(chr14:92485881)   | <i>TRIP11</i> (intronic)                                            | FEV <sub>1</sub>      | G               | T               | 0.64                     | -0.022 | 0.006 | 4.02E-04 | 0.64                     | 0.98           | -0.013 | 0.031 | 6.75E-01        |
| rs117068593<br>(chr14:93118229) | <i>RIN3</i> (exonic)                                                | FEV <sub>1</sub>      | C               | T               | 0.81                     | -0.027 | 0.008 | 5.68E-04 | 0.82                     | 0.94           | -0.021 | 0.039 | 5.90E-01        |
| rs12149828<br>(chr16:10706328)  | <i>EMP2</i> (dist=31789),<br><i>TEKT5</i> (dist=15033)              | FEV <sub>1</sub> /FVC | G               | A               | 0.83                     | 0.035  | 0.008 | 3.33E-05 | 0.83                     | 0.91           | -0.007 | 0.039 | 8.58E-01        |
| rs113473882<br>(chr19:41124155) | <i>LTBP4</i> (intronic)                                             | FEV <sub>1</sub> /FVC | T               | C               | 0.99                     | -0.138 | 0.028 | 9.94E-07 | 0.99                     | 0.76           | 0.177  | 0.147 | 2.29E-01        |
| rs134041<br>(chr22:28056338)    | <i>MIAT</i> (dist=983898), <i>MN1</i><br>(dist=87927)               | FEV <sub>1</sub>      | T               | C               | 0.44                     | -0.018 | 0.006 | 4.12E-03 | 0.44                     | 0.99           | 0.003  | 0.029 | 9.18E-01        |
| rs7050036<br>(chrX:15964845)    | <i>AP1S2</i> (dist=91708),<br><i>GRPR</i> (dist=176579)             | FEV <sub>1</sub> /FVC | T               | A               | 0.39                     | -0.013 | 0.005 | 1.60E-02 | 0.40                     | 0.98           | 0.017  | 0.023 | 4.70E-01        |

## b) Effect of novel signals on ever smokers and never smokers in stage 1

Stage 1 results for genome-wide significant associations ( $P < 5 \times 10^{-8}$ ) with either FEV<sub>1</sub>, FEV<sub>1</sub>/FVC or FVC separately in ever smokers and never smokers, and the interaction  $P$  value are shown. Chr., chromosome.

| rs number<br>(chr:position)     | Coded<br>allele | Measure               | Ever smokers |       |          | Never smokers |       |          | Interaction |
|---------------------------------|-----------------|-----------------------|--------------|-------|----------|---------------|-------|----------|-------------|
|                                 |                 |                       | Beta         | SE    | P        | Beta          | SE    | P        | P           |
| rs6681426<br>(chr1:150586971)   | G               | FEV <sub>1</sub>      | 0.038        | 0.010 | 2.54E-04 | 0.049         | 0.012 | 2.07E-05 | 4.82E-01    |
| rs201204531<br>(chr1:219963090) | A               | FEV <sub>1</sub> /FVC | -0.039       | 0.010 | 1.94E-04 | -0.036        | 0.012 | 2.63E-03 | 8.32E-01    |
| rs61067109<br>(chr2:18292452)   | G               | FEV <sub>1</sub> /FVC | -0.043       | 0.012 | 3.61E-04 | -0.054        | 0.013 | 4.04E-05 | 5.51E-01    |
| rs6441207<br>(chr3:158282459)   | C               | FVC                   | 0.029        | 0.010 | 5.38E-03 | 0.042         | 0.012 | 3.02E-04 | 4.09E-01    |
| rs6856422<br>(chr4:106841962)   | G               | FEV <sub>1</sub> /FVC | -0.043       | 0.011 | 1.02E-04 | -0.044        | 0.012 | 4.27E-04 | 9.69E-01    |
| rs148274477<br>(chr6:142838173) | C               | FEV <sub>1</sub> /FVC | -0.195       | 0.037 | 1.01E-07 | -0.118        | 0.039 | 2.51E-03 | 1.51E-01    |
| rs34886460<br>(chr9:119359372)  | T               | FEV <sub>1</sub> /FVC | 0.027        | 0.010 | 6.96E-03 | 0.055         | 0.011 | 7.06E-07 | 6.27E-02    |
| rs2274116<br>(chr9:139094805)   | C               | FVC                   | 0.038        | 0.011 | 8.04E-04 | 0.041         | 0.013 | 1.19E-03 | 8.75E-01    |
| rs11383346<br>(chr12:28283187)  | A               | FVC                   | -0.036       | 0.010 | 5.67E-04 | -0.049        | 0.011 | 1.54E-05 | 3.91E-01    |
| rs10850377<br>(chr12:115201436) | G               | FEV <sub>1</sub>      | -0.052       | 0.011 | 1.66E-06 | -0.042        | 0.012 | 3.20E-04 | 5.35E-01    |
| rs7155279<br>(chr14:92485881)   | G               | FEV <sub>1</sub>      | -0.049       | 0.010 | 3.11E-06 | -0.035        | 0.011 | 2.47E-03 | 3.66E-01    |
| rs117068593<br>(chr14:93118229) | C               | FEV <sub>1</sub>      | -0.053       | 0.014 | 7.86E-05 | -0.038        | 0.015 | 1.09E-02 | 4.45E-01    |
| rs12149828<br>(chr16:10706328)  | G               | FEV <sub>1</sub> /FVC | 0.057        | 0.014 | 3.87E-05 | 0.038         | 0.015 | 1.41E-02 | 3.45E-01    |
| rs113473882<br>(chr19:41124155) | T               | FEV <sub>1</sub> /FVC | -0.206       | 0.044 | 3.32E-06 | -0.135        | 0.048 | 5.42E-03 | 2.78E-01    |
| rs134041<br>(chr22:28056338)    | T               | FEV <sub>1</sub>      | -0.043       | 0.010 | 2.25E-05 | -0.045        | 0.011 | 4.93E-05 | 8.88E-01    |
| rs7050036<br>(chrX:15964845)    | T               | FEV <sub>1</sub> /FVC | -0.048       | 0.011 | 1.72E-05 | -0.033        | 0.015 | 3.16E-02 | 4.46E-01    |

### c) Associations with smoking behaviour in UK BiLEVE for novel signals

Association of the 16 sentinel variants with heavy vs. never smoking status in UK BiLEVE (N heavy=24,457, N never=24,474).  $P$  that met a Bonferroni corrected threshold for 16 tests ( $P < 3.13 \times 10^{-3}$ ) are highlighted in bold. Chr., chromosome.

| rs number (chr: position)    | Coded allele | Other allele | MAF  | Imputation quality | Beta   | SE    | P               |
|------------------------------|--------------|--------------|------|--------------------|--------|-------|-----------------|
| rs6681426 (chr1:150586971)   | A            | G            | 0.35 | 1.00               | -0.003 | 0.013 | 8.07E-01        |
| rs201204531 (chr1:219963090) | ATG          | A            | 0.38 | 0.99               | 0.042  | 0.013 | <b>1.54E-03</b> |
| rs61067109 (chr2:18292452)   | A            | G            | 0.23 | 1.00               | -0.007 | 0.015 | 6.33E-01        |
| rs6441207 (chr3:158282459)   | T            | C            | 0.40 | 1.00               | -0.008 | 0.013 | 5.30E-01        |
| rs6856422 (chr4:106841962)   | T            | G            | 0.45 | 0.95               | -0.010 | 0.013 | 4.50E-01        |
| rs148274477 (chr6:142838173) | T            | C            | 0.03 | 0.98               | -0.067 | 0.040 | 9.45E-02        |
| rs10512249 (chr9:98256309)   | A            | G            | 0.10 | 0.99               | 0.034  | 0.022 | 1.16E-01        |
| rs34886460 (chr9:119359372)  | TA           | T            | 0.47 | 1.00               | 0.020  | 0.013 | 1.23E-01        |
| rs2274116 (chr9:139094805)   | T            | C            | 0.34 | 0.98               | -0.018 | 0.014 | 1.75E-01        |
| rs11383346 (chr12:28283187)  | AT           | A            | 0.41 | 1.00               | -0.029 | 0.013 | 2.47E-02        |
| rs10850377 (chr12:115201436) | A            | G            | 0.34 | 0.98               | -0.019 | 0.014 | 1.52E-01        |
| rs7155279 (chr14:92485881)   | T            | G            | 0.36 | 1.00               | 0.015  | 0.013 | 2.63E-01        |
| rs117068593 (chr14:93118229) | T            | C            | 0.19 | 0.98               | -0.003 | 0.016 | 8.50E-01        |
| rs12149828 (chr16:10706328)  | A            | G            | 0.16 | 0.94               | -0.017 | 0.018 | 3.53E-01        |
| rs113473882 (chr19:41124155) | C            | T            | 0.01 | 0.95               | -0.150 | 0.067 | 2.55E-02        |
| rs134041 (chr22:28056338)    | C            | T            | 0.44 | 0.98               | -0.007 | 0.013 | 5.80E-01        |
| rs7050036 (chrX:15964845)    | A            | T            | 0.39 | 0.98               | 0.000  | 0.011 | 9.69E-01        |

#### **d) Associations of top hits with other traits**

The GWAS catalog<sup>101</sup> was searched for variants in 2Mb regions centred on the sentinel variant for the 16 sentinel variants. Variants that were genome-wide significant ( $P < 5 \times 10^{-8}$ ) in the GWAS catalog<sup>101</sup> and were in LD ( $r^2 > 0.3$ ) with the sentinel variants, or were in genes that contained at least one variant in LD ( $r^2 > 0.3$ ) with the sentinel variants were selected. Chr., chromosome.

| Sentinel rs number<br>(chr:position) | rs number<br>(chr:position)    | R <sup>2</sup> with<br>sentinel | PubMed id | Trait                                      | Gene Symbol                                       | P        |
|--------------------------------------|--------------------------------|---------------------------------|-----------|--------------------------------------------|---------------------------------------------------|----------|
| rs6681426<br>(chr1:150586971)        | rs2230061<br>(chr1:150727539)  | 6.44E-01                        | 24064335  | Fat body mass                              | <i>CTSS</i>                                       | 4.00E-08 |
| rs6681426<br>(chr1:150586971)        | rs7412746<br>(chr1:150860471)  | 4.09E-01                        | 21983785  | Melanoma                                   | <i>ARNT, SETDB1, LASS2, ANXA9, MCL1, CTSK</i>     | 9.00E-11 |
| rs6681426<br>(chr1:150586971)        | rs267734<br>(chr1:150951477)   | 1.30E-01                        | 20383146  | Chronic kidney disease                     | <i>ANXA9, FAM63A, PRUNE, BNIPL, LASS2, SETDB1</i> | 1.00E-12 |
| rs6681426<br>(chr1:150586971)        | rs267733<br>(chr1:150958836)   | 8.34E-02                        | 24097068  | LDL cholesterol                            | <i>ANXA9, CERS2</i>                               | 5.00E-09 |
| rs201204531<br>(chr1:219963090)      | rs2820443<br>(chr1:219753509)  | 2.93E-02                        | 23754948  | Sexual dimorphism in anthropometric traits | <i>LYPLAL1, SLC30A10, ZC3H11B</i>                 | 7.00E-16 |
| rs6441207<br>(chr3:158282459)        | rs2362965<br>(chr3:158109379)  | 6.33E-01                        | 23563607  | Height                                     | <i>RSRC1, SHOX2</i>                               | 2.00E-09 |
| rs6856422<br>(chr4:106841962)        | rs11727189<br>(chr4:106619140) | 7.48E-02                        | 20010835  | Pulmonary function                         | <i>INTS12, NPNT, FLJ20184, GSTCD</i>              | 5.00E-17 |
| rs6856422<br>(chr4:106841962)        | rs10516526<br>(chr4:106688904) | 7.50E-02                        | 20010834  | Pulmonary function                         | <i>GSTCD</i>                                      | 2.00E-23 |
| rs6856422<br>(chr4:106841962)        | rs17331332<br>(chr4:106808107) | 7.89E-02                        | 23284291  | Pulmonary function (interaction)           | <i>INTS12, GSTCD, NPNT</i>                        | 1.00E-16 |
| rs148274477<br>(chr6:142838173)      | rs7741741<br>(chr6:142655801)  | 6.51E-02                        | 23563607  | Height                                     | <i>GPR126</i>                                     | 1.00E-20 |
| rs148274477<br>(chr6:142838173)      | rs6570507<br>(chr6:142679572)  | 5.94E-02                        | 23666238  | Scoliosis                                  | <i>GPR126</i>                                     | 4.00E-14 |
| rs148274477<br>(chr6:142838173)      | rs6570507<br>(chr6:142679572)  | 5.94E-02                        | 19343178  | Height                                     | <i>GPR126</i>                                     | 4.00E-11 |
| rs148274477<br>(chr6:142838173)      | rs4896582<br>(chr6:142703877)  | 5.52E-02                        | 18391950  | Height                                     | <i>GPR126</i>                                     | 2.00E-18 |
| rs148274477<br>(chr6:142838173)      | rs3817928<br>(chr6:142750516)  | 1.02E-01                        | 23284291  | Pulmonary function (interaction)           | <i>GPR126</i>                                     | 3.00E-12 |
| rs148274477<br>(chr6:142838173)      | rs3817928<br>(chr6:142750516)  | 1.02E-01                        | 20010835  | Pulmonary function                         | <i>GPR126</i>                                     | 1.00E-09 |
| rs148274477<br>(chr6:142838173)      | rs3748069<br>(chr6:142767633)  | 6.58E-02                        | 18391951  | Height                                     | <i>GPR126</i>                                     | 5.00E-14 |
| rs148274477<br>(chr6:142838173)      | rs7763064<br>(chr6:142797289)  | 6.47E-02                        | 20881960  | Height                                     | <i>GPR126</i>                                     | 1.00E-33 |
| rs34886460<br>(chr9:119359372)       | rs6478241<br>(chr9:119252629)  | 5.27E-02                        | 23793025  | Migraine - clinic-based                    | <i>ASTN2</i>                                      | 1.00E-09 |
| rs34886460<br>(chr9:119359372)       | rs6478241<br>(chr9:119252629)  | 5.27E-02                        | 22683712  | Migraine                                   | <i>ASTN2</i>                                      | 4.00E-08 |
| rs2274116<br>(chr9:139094805)        | rs7860634<br>(chr9:139089679)  | 3.74E-01                        | 23408906  | Thyroid hormone levels                     | <i>LHX3</i>                                       | 2.00E-14 |
| rs2274116<br>(chr9:139094805)        | rs7849585<br>(chr9:139111870)  | 1.51E-01                        | 20881960  | Height                                     | <i>QSOX2</i>                                      | 5.00E-14 |
| rs2274116<br>(chr9:139094805)        | rs12338076<br>(chr9:139121740) | 1.55E-01                        | 20189936  | Height                                     | <i>LHX3, QSOX2</i>                                | 2.00E-08 |
| rs11383346<br>(chr12:28283187)       | rs2638953<br>(chr12:28534415)  | 3.00E-01                        | 20881960  | Height                                     | <i>CCDC91</i>                                     | 7.00E-17 |

| Sentinel rs number<br>(chr:position) | rs number<br>(chr:position)    | R <sup>2</sup> with<br>sentinel | PubMed id | Trait                                                      | Gene Symbol                        | P        |
|--------------------------------------|--------------------------------|---------------------------------|-----------|------------------------------------------------------------|------------------------------------|----------|
| rs11383346<br>(chr12:28283187)       | rs10843164<br>(chr12:28569714) | 2.89E-01                        | 23563607  | Height                                                     | <i>CCDC91</i>                      | 6.00E-12 |
| rs7155279<br>(chr14:92485881)        | rs7153027<br>(chr14:92427222)  | 7.41E-01                        | 18391951  | Height                                                     | <i>TRIP11, FBLN5, ATXN3, CPSF2</i> | 1.00E-10 |
| rs7155279<br>(chr14:92485881)        | rs8007661<br>(chr14:92459958)  | 6.45E-01                        | 18391950  | Height                                                     | <i>TRIP11, ATXN3</i>               | 6.00E-10 |
| rs7155279<br>(chr14:92485881)        | rs7155279<br>(chr14:92485881)  | 1.00E+00                        | 20881960  | Height                                                     | <i>TRIP11</i>                      | 1.00E-10 |
| rs117068593<br>(chr14:93118229)      | rs10498633<br>(chr14:92926952) | 2.75E-05                        | 24162737  | Alzheimer's disease (late onset)                           | <i>SLC24A4, RIN3</i>               | 6.00E-09 |
| rs117068593<br>(chr14:93118229)      | rs10498635<br>(chr14:93103309) | 9.39E-01                        | 21623375  | Paget's disease                                            | <i>RIN3</i>                        | 3.00E-11 |
| rs117068593<br>(chr14:93118229)      | rs754388<br>(chr14:93115410)   | 9.94E-01                        | 24621683  | Chronic obstructive pulmonary disease (moderate to severe) | <i>RIN3</i>                        | 5.00E-09 |
| rs117068593<br>(chr14:93118229)      | rs754388<br>(chr14:93115410)   | 9.94E-01                        | 24945404  | Bone mineral density (paediatric, total body less head)    | <i>RIN3</i>                        | 3.00E-09 |
| rs117068593<br>(chr14:93118229)      | rs754388<br>(chr14:93115410)   | 9.94E-01                        | 24945404  | Bone mineral density (paediatric, lower limb)              | <i>RIN3</i>                        | 1.00E-10 |
| rs113473882<br>(chr19:41124155)      | rs28493229<br>(chr19:41224204) | 6.63E-04                        | 22081228  | Kawasaki disease                                           | <i>ITPKC</i>                       | 2.00E-12 |
| rs113473882<br>(chr19:41124155)      | rs2233152<br>(chr19:41281016)  | 5.98E-04                        | 22446962  | Kawasaki disease                                           | <i>NUMBL, MIA</i>                  | 4.00E-10 |
| rs113473882<br>(chr19:41124155)      | rs7937<br>(chr19:41302706)     | 5.19E-03                        | 22080838  | Chronic obstructive pulmonary disease                      | <i>RAB4B, EGLN2, CYP2A6</i>        | 3.00E-09 |

**Supplementary Table 6** List of 49 lung function signals detected to date

Variants associated with FEV<sub>1</sub>, FEV<sub>1</sub>/FVC or FVC in lung function GWAS to date are presented. The study in which each variant was firstly identified is indicated ("Identified in"), and the results presented ("Results from") correspond to the study with largest sample size available for the previously discovered variants and to the current study for the novel variants. Effect sizes correspond to inverse normally transformed lung function traits in all instances except for those FVC results extracted from Loth 2014<sup>4</sup>, which correspond to ml. Previous studies referred to in the table are: Wilk\_2009<sup>1</sup>, Repapi\_2010<sup>5</sup>, Hancock\_2010<sup>2</sup>, Soler\_Artigas\_2011<sup>3</sup> and Loth\_2014<sup>4</sup>.

| rs number (chr: position)    | Gene (closest)       | Measure  | Identified in              | Results from       | Alleles | Coded allele | Coded allele freq | Beta    | SE    | Pval     |
|------------------------------|----------------------|----------|----------------------------|--------------------|---------|--------------|-------------------|---------|-------|----------|
| rs2284746 (chr1:17306675)    | <i>MFAP2</i>         | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | C/G     | G            | 0.58              | -0.040  | 0.005 | 7.50E-16 |
| rs6681426 (chr1:150586971)   | <i>ENSA</i>          | FEV1     | current                    | current            | A/G     | G            | 0.36              | 0.029   | 0.005 | 4.35E-09 |
| rs993925 (chr1:218860068)    | <i>TGFB2</i>         | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | C/T     | T            | 0.42              | 0.034   | 0.006 | 1.16E-08 |
| rs201204531 (chr1:219963090) | <i>RNU5F-1</i>       | FEV1/FVC | current                    | current            | ATG/A   | A            | 0.41              | -0.031  | 0.005 | 2.68E-10 |
| rs61067109 (chr2:18292452)   | <i>KCNS3</i>         | FEV1/FVC | current                    | current            | A/G     | G            | 0.77              | -0.045  | 0.006 | 1.40E-15 |
| rs1430193 (chr2:56120853)    | <i>EFEMP1</i>        | FVC      | Loth_2014                  | Loth_2014          | A/T     | T            | 0.37              | -21.125 | 2.999 | 1.86E-12 |
| rs2571445 (chr2:218683154)   | <i>TNS1</i>          | FEV1     | Repapi_2010                | Soler_Artigas_2011 | A/G     | G            | 0.62              | 0.047   | 0.007 | 9.83E-11 |
| rs12477314 (chr2:239877148)  | <i>HDAC4</i>         | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | C/T     | T            | 0.13              | 0.041   | 0.006 | 1.68E-12 |
| rs1529672 (chr3:25520582)    | <i>RARB</i>          | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | A/C     | C            | 0.86              | -0.048  | 0.006 | 3.97E-14 |
| rs6441207 (chr3:158282459)   | <i>RP11-538P18.2</i> | FVC      | current                    | current            | T/C     | C            | 0.59              | 0.036   | 0.005 | 1.27E-13 |
| rs1344555 (chr3:169300219)   | <i>MECOM</i>         | FEV1     | Soler_Artigas_2011         | Soler_Artigas_2011 | C/T     | T            | 0.17              | -0.034  | 0.006 | 2.65E-08 |
| rs2045517 (chr4:89870964)    | <i>FAM13A</i>        | FEV1/FVC | Hancock_2010               | Soler_Artigas_2011 | C/T     | T            | 0.36              | -0.047  | 0.007 | 2.00E-11 |
| rs10516526 (chr4:106688904)  | <i>GSTCD</i>         | FEV1     | Repapi_2010 & Hancock_2010 | Soler_Artigas_2011 | A/G     | G            | 0.08              | 0.108   | 0.014 | 4.75E-14 |
| rs6856422 (chr4:106841962)   | <i>NPNT</i>          | FEV1/FVC | current                    | current            | T/G     | G            | 0.53              | -0.051  | 0.005 | 1.51E-23 |
| rs11100860 (chr4:145479139)  | <i>HHIP</i>          | FEV1/FVC | Wilk_2009                  | Soler_Artigas_2011 | A/G     | G            | 0.43              | 0.064   | 0.007 | 6.81E-20 |
| rs153916 (chr5:95036700)     | <i>SPATA9</i>        | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | C/T     | T            | 0.52              | -0.031  | 0.005 | 2.12E-08 |
| rs1985524 (chr5:147847788)   | <i>HTR4</i>          | FEV1     | Repapi_2010                | Soler_Artigas_2011 | C/G     | G            | 0.61              | -0.048  | 0.007 | 3.06E-11 |
| rs11134779 (chr5:156936766)  | <i>ADAM19</i>        | FEV1/FVC | Hancock_2010               | Soler_Artigas_2011 | A/G     | G            | 0.31              | -0.042  | 0.007 | 6.01E-09 |

| rs number (chr: position)    | Gene (closest)   | Measure  | Identified in              | Results from       | Alleles | Coded allele | Coded allele freq | Beta    | SE    | Pval     |
|------------------------------|------------------|----------|----------------------------|--------------------|---------|--------------|-------------------|---------|-------|----------|
| rs6923462 (chr6:7801112)     | <i>BMP6</i>      | FVC      | Loth_2014                  | Loth_2014          | C/T     | T            | 0.84              | 30.883  | 4.288 | 5.89E-13 |
| rs6903823 (chr6:28322296)    | <i>ZKSCAN3</i>   | FEV1     | Soler_Artigas_2011         | Soler_Artigas_2011 | A/G     | G            | 0.19              | -0.037  | 0.006 | 2.18E-10 |
| rs2857595 (chr6:31568469)    | <i>NCR3</i>      | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | A/G     | G            | 0.79              | 0.037   | 0.006 | 2.28E-10 |
| rs2070600 (chr6:32151443)    | <i>AGER</i>      | FEV1/FVC | Repapi_2010 & Hancock_2010 | Soler_Artigas_2011 | C/T     | T            | 0.05              | 0.126   | 0.016 | 9.07E-15 |
| rs2798641 (chr6:109268050)   | <i>ARMC2</i>     | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | C/T     | T            | 0.13              | -0.041  | 0.007 | 8.35E-09 |
| rs148274477 (chr6:142838173) | <i>GPR126</i>    | FEV1/FVC | current                    | current            | T/C     | C            | 0.98              | -0.162  | 0.015 | 9.58E-26 |
| rs262129 (chr6:142853144)    | <i>LOC153910</i> | FEV1/FVC | Hancock_2010               | Soler_Artigas_2011 | A/G     | G            | 0.26              | 0.056   | 0.008 | 2.91E-13 |
| rs16909859 (chr9:98204792)   | <i>PTCH1</i>     | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | A/G     | G            | 0.89              | 0.080   | 0.013 | 7.45E-10 |
| rs16909898 (chr9:98231008)   | <i>PTCH1</i>     | FEV1/FVC | Hancock_2010               | Soler_Artigas_2011 | A/G     | G            | 0.85              | -0.072  | 0.012 | 3.94E-09 |
| rs34886460 (chr9:119359372)  | <i>ASTN2</i>     | FEV1/FVC | current                    | current            | TA/T    | T            | 0.53              | 0.031   | 0.005 | 4.72E-11 |
| rs2274116 (chr9:139094805)   | <i>LHX3</i>      | FVC      | current                    | current            | T/C     | C            | 0.67              | 0.039   | 0.005 | 5.55E-14 |
| rs7068966 (chr10:12277992)   | <i>CDC123</i>    | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | C/T     | T            | 0.43              | 0.033   | 0.005 | 6.13E-13 |
| rs11001819 (chr10:78315224)  | <i>C10orf11</i>  | FEV1     | Soler_Artigas_2011         | Soler_Artigas_2011 | A/G     | G            | 0.50              | -0.029  | 0.004 | 2.98E-12 |
| rs4237643 (chr11:43648368)   | <i>HSD17B12</i>  | FVC      | Loth_2014                  | Loth_2014          | T/G     | T            | 0.31              | -16.666 | 3.023 | 3.53E-08 |
| rs2863171 (chr11:45250732)   | <i>PRDM11</i>    | FVC      | Loth_2014                  | Loth_2014          | A/C     | C            | 0.16              | 23.924  | 3.906 | 8.97E-10 |
| rs11383346 (chr12:28283187)  | <i>CCDC91</i>    | FVC      | current                    | current            | AT/A    | A            | 0.41              | -0.042  | 0.005 | 9.52E-18 |
| rs11172113 (chr12:57527283)  | <i>LRP1</i>      | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | C/T     | T            | 0.66              | -0.032  | 0.006 | 1.24E-08 |
| rs1036429 (chr12:96271428)   | <i>CCDC38</i>    | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | C/T     | T            | 0.25              | 0.038   | 0.006 | 2.30E-11 |
| rs10850377 (chr12:115201436) | <i>TBX3</i>      | FEV1     | current                    | current            | A/G     | G            | 0.67              | -0.035  | 0.005 | 2.50E-12 |
| rs7155279 (chr14:92485881)   | <i>TRIP11</i>    | FEV1     | current                    | current            | T/G     | G            | 0.64              | -0.030  | 0.005 | 1.41E-09 |
| rs117068593 (chr14:93118229) | <i>RIN3</i>      | FEV1     | current                    | current            | T/C     | C            | 0.82              | -0.035  | 0.006 | 2.25E-08 |
| rs8033889 (chr15:71680080)   | <i>THSD4</i>     | FEV1/FVC | Repapi_2010 & Hancock_2010 | Soler_Artigas_2011 | G/T     | T            | 0.14              | -0.072  | 0.008 | 2.03E-17 |
| rs12149828 (chr16:10706328)  | <i>EMP2</i>      | FEV1/FVC | current                    | current            | A/G     | G            | 0.83              | 0.040   | 0.007 | 7.65E-10 |
| rs12447804 (chr16:58075282)  | <i>MMP15</i>     | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | C/T     | T            | 0.24              | -0.038  | 0.007 | 3.59E-08 |
| rs2865531 (chr16:75390316)   | <i>CFDP1</i>     | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | A/T     | T            | 0.47              | 0.031   | 0.005 | 1.77E-11 |
| rs1079572 (chr16:78187138)   | <i>WVOX</i>      | FVC      | Loth_2014                  | Loth_2014          | G/A     | G            | 0.42              | 16.258  | 2.837 | 9.95E-09 |
| rs6501431 (chr17:68976415)   | <i>KCNJ2</i>     | FVC      | Loth_2014                  | Loth_2014          | C/T     | T            | 0.80              | 23.053  | 3.884 | 2.94E-09 |
| rs113473882 (chr19:41124155) | <i>LTBP4</i>     | FEV1/FVC | current                    | current            | C/T     | T            | 0.98              | -0.153  | 0.021 | 9.95E-13 |
| rs9978142 (chr21:35652239)   | <i>KCNE2</i>     | FEV1/FVC | Soler_Artigas_2011         | Soler_Artigas_2011 | A/T     | T            | 0.22              | -0.043  | 0.008 | 2.65E-08 |

| rs number (chr: position) | Gene (closest) | Measure  | Identified in | Results from | Alleles | Coded allele | Coded allele freq | Beta   | SE    | Pval     |
|---------------------------|----------------|----------|---------------|--------------|---------|--------------|-------------------|--------|-------|----------|
| rs134041 (chr22:28056338) | <i>MN1</i>     | FEV1     | current       | current      | C/T     | T            | 0.43              | -0.028 | 0.005 | 3.03E-09 |
| rs7050036 (chrX:15964845) | <i>AP1S2</i>   | FEV1/FVC | current       | current      | A/T     | T            | 0.38              | -0.023 | 0.004 | 4.14E-08 |

**Supplementary Table 7** Proportion of variance explained

Stage 1 results for the 33 previously discovered signals<sup>1-5</sup> and the 16 novel signals are shown with the proportion of the variance of the lung function traits that they explain ( $r^2$ ), separately for FEV<sub>1</sub>, FEV<sub>1</sub>/FVC and FVC. Additive polygenic variance is estimated assuming a heritability for lung function of 40%<sup>103-105</sup>. Chr., chromosome; freq., frequency.

a. FEV<sub>1</sub>

| rs number (chr: position)                                   | Closest gene     | Coded allele | Non coded allele | Coded allele freq. | Beta (SE)      | P        | N     | r <sup>2</sup> (%) |
|-------------------------------------------------------------|------------------|--------------|------------------|--------------------|----------------|----------|-------|--------------------|
| <b>Known</b>                                                |                  |              |                  |                    |                |          |       |                    |
| rs2284746 (chr1:17306675)                                   | <i>MFAP2</i>     | C            | G                | 0.50               | -0.011 (0.008) | 1.40E-01 | 36224 | 0.006              |
| rs993925 (chr1:218860068)                                   | <i>TGFB2</i>     | C            | T                | 0.66               | -0.016 (0.008) | 5.32E-02 | 35599 | 0.010              |
| rs1430193 (chr2:56120853)                                   | <i>EFEMP1</i>    | A            | T                | 0.61               | 0.02 (0.008)   | 1.42E-02 | 35824 | 0.017              |
| rs2571445 (chr2:218683154)                                  | <i>TNS1</i>      | A            | G                | 0.40               | -0.034 (0.008) | 8.56E-06 | 37553 | 0.053              |
| rs12477314 (chr2:239877148)                                 | <i>HDAC4</i>     | C            | T                | 0.80               | -0.032 (0.009) | 5.28E-04 | 37932 | 0.032              |
| rs1529672 (chr3:25520582)                                   | <i>RARB</i>      | C            | A                | 0.83               | -0.025 (0.01)  | 1.17E-02 | 36309 | 0.018              |
| rs1344555 (chr3:169300219)                                  | <i>MECOM</i>     | C            | T                | 0.79               | 0.036 (0.01)   | 1.62E-04 | 35867 | 0.040              |
| rs2045517 (chr4:89870964)                                   | <i>FAM13A</i>    | C            | T                | 0.59               | 0 (0.008)      | 9.52E-01 | 38095 | 0.000              |
| rs10516526 (chr4:106688904)                                 | <i>GSTCD</i>     | A            | G                | 0.94               | -0.100 (0.016) | 1.52E-10 | 37284 | 0.110              |
| rs11100860 (chr4:145479139)                                 | <i>HHIP</i>      | A            | G                | 0.58               | -0.028 (0.008) | 1.96E-04 | 38063 | 0.036              |
| rs153916 (chr5:95036700)                                    | <i>SPATA9</i>    | C            | T                | 0.44               | -0.004 (0.008) | 5.90E-01 | 37448 | 0.001              |
| rs1985524 (chr5:147847788)                                  | <i>HTR4</i>      | G            | C                | 0.54               | -0.045 (0.008) | 3.11E-09 | 37265 | 0.094              |
| rs11134779 (chr5:156936766)                                 | <i>ADAM19</i>    | A            | G                | 0.66               | 0.029 (0.008)  | 1.85E-04 | 38090 | 0.037              |
| rs6923462 (chr6:7801112)                                    | <i>BMP6</i>      | T            | C                | 0.84               | 0.037 (0.01)   | 3.00E-04 | 37005 | 0.035              |
| rs6903823 (chr6:28322296)                                   | <i>ZKSCAN3</i>   | A            | G                | 0.78               | 0.035 (0.01)   | 3.71E-04 | 37973 | 0.033              |
| rs114327456 (chr6:31568469)                                 | <i>NCR3</i>      | G            | A                | 0.78               | 0.036 (0.01)   | 3.22E-04 | 34997 | 0.037              |
| rs114177847 (chr6:32151443)                                 | <i>AGER</i>      | C            | T                | 0.95               | -0.03 (0.021)  | 1.63E-01 | 25796 | 0.008              |
| rs2798641 (chr6:109268050)                                  | <i>ARMC2</i>     | C            | T                | 0.82               | 0.026 (0.01)   | 8.57E-03 | 37706 | 0.018              |
| rs262129 (chr6:142853144)                                   | <i>LOC153910</i> | A            | G                | 0.70               | -0.01 (0.008)  | 2.24E-01 | 37585 | 0.004              |
| rs16909859 (chr9:98204792)                                  | <i>PTCH1</i>     | G            | A                | 0.92               | -0.007 (0.014) | 6.06E-01 | 33748 | 0.001              |
| rs16909898 (chr9:98231008)                                  | <i>PTCH1</i>     | A            | G                | 0.90               | -0.031 (0.013) | 1.53E-02 | 36168 | 0.016              |
| rs7068966 (chr10:12277992)                                  | <i>CDC123</i>    | C            | T                | 0.48               | -0.037 (0.008) | 9.53E-07 | 37832 | 0.063              |
| rs11001819 (chr10:78315224)                                 | <i>C10orf11</i>  | G            | A                | 0.52               | -0.027 (0.008) | 3.44E-04 | 38018 | 0.034              |
| rs4237643 (chr11:43648368)                                  | <i>HSD17B12</i>  | T            | G                | 0.30               | -0.026 (0.008) | 1.27E-03 | 38018 | 0.027              |
| rs2863171 (chr11:45250732)                                  | <i>PRDM11</i>    | A            | C                | 0.84               | -0.032 (0.01)  | 2.11E-03 | 38138 | 0.025              |
| rs11172113 (chr12:57527283)                                 | <i>LRP1</i>      | T            | C                | 0.60               | -0.011 (0.008) | 1.46E-01 | 37724 | 0.006              |
| rs1036429 (chr12:96271428)                                  | <i>CCDC38</i>    | T            | C                | 0.19               | 0.011 (0.01)   | 2.29E-01 | 38123 | 0.004              |
| rs8033889 (chr15:71680080)                                  | <i>THSD4</i>     | G            | T                | 0.78               | 0.032 (0.009)  | 3.29E-04 | 38080 | 0.034              |
| rs12447804 (chr16:58075282)                                 | <i>MMP15</i>     | C            | T                | 0.77               | 0.008 (0.009)  | 3.89E-01 | 37782 | 0.002              |
| rs2865531 (chr16:75390316)                                  | <i>CFDP1</i>     | T            | A                | 0.41               | 0.025 (0.008)  | 1.24E-03 | 37942 | 0.027              |
| rs1079572 (chr16:78187138)                                  | <i>WWOX</i>      | G            | A                | 0.43               | 0.016 (0.008)  | 3.41E-02 | 37809 | 0.012              |
| rs6501431 (chr17:68976415)                                  | <i>KCNJ2</i>     | C            | T                | 0.21               | -0.021 (0.009) | 2.35E-02 | 37869 | 0.014              |
| rs9978142 (chr21:35652239)                                  | <i>KCNE2</i>     | A            | T                | 0.85               | 0.010 (0.011)  | 3.46E-01 | 37633 | 0.002              |
| <b>Total r<sup>2</sup> for known variants</b>               |                  |              |                  |                    |                |          |       | <b>0.855</b>       |
| <b>Total additive polygenic variance for known variants</b> |                  |              |                  |                    |                |          |       | <b>2.138</b>       |
| <b>New</b>                                                  |                  |              |                  |                    |                |          |       |                    |
| rs6681426 (chr1:150586971)                                  | <i>ENSA</i>      | G            | A                | 0.36               | 0.042 (0.008)  | 1.07E-07 | 37944 | 0.074              |
| rs201204531 (chr1:219963090)                                | <i>RNU5F-1</i>   | A            | ATG              | 0.41               | -0.007 (0.008) | 3.75E-01 | 34887 | 0.002              |

| rs number (chr: position)                                    | Closest gene | Coded allele | Non coded allele | Coded allele freq. | Beta (SE)      | P        | N     | r <sup>2</sup> (%) |
|--------------------------------------------------------------|--------------|--------------|------------------|--------------------|----------------|----------|-------|--------------------|
| rs61067109 (chr2:18292452)                                   | KCNS3        | G            | A                | 0.77               | -0.039 (0.009) | 1.83E-05 | 37433 | 0.049              |
| rs6441207 (chr3:158282459)                                   | AK097794     | C            | T                | 0.59               | 0.029 (0.008)  | 2.07E-04 | 36426 | 0.038              |
| rs6856422 (chr4:106841962)                                   | NPNT         | G            | T                | 0.53               | -0.045 (0.008) | 6.22E-08 | 31460 | 0.093              |
| rs148274477 (chr6:142838173)                                 | LOC153910    | C            | T                | 0.98               | 0.010 (0.027)  | 7.07E-01 | 30318 | 0.000              |
| rs34886460 (chr9:119359372)                                  | ASTN2        | T            | TA               | 0.53               | 0.023 (0.008)  | 2.85E-03 | 37583 | 0.024              |
| rs2274116 (chr9:139094805)                                   | LHX3         | C            | T                | 0.67               | 0.029 (0.009)  | 6.27E-04 | 32226 | 0.036              |
| rs11383346 (chr12:28283187)                                  | CCDC91       | A            | AT               | 0.41               | -0.039 (0.008) | 3.41E-07 | 37510 | 0.069              |
| rs10850377 (chr12:115201436)                                 | TBX3         | G            | A                | 0.67               | -0.047 (0.008) | 6.68E-09 | 37268 | 0.090              |
| rs7155279 (chr14:92485881)                                   | TRIP11       | G            | T                | 0.64               | -0.041 (0.008) | 1.39E-07 | 37691 | 0.074              |
| rs117068593 (chr14:93118229)                                 | RIN3         | C            | T                | 0.82               | -0.048 (0.01)  | 2.72E-06 | 34496 | 0.064              |
| rs12149828 (chr16:10706328)                                  | TEKT5        | G            | A                | 0.83               | 0.037 (0.01)   | 3.38E-04 | 34022 | 0.038              |
| rs113473882 (chr19:41124155)                                 | LTBP4        | T            | C                | 0.98               | -0.029 (0.033) | 3.78E-01 | 32220 | 0.002              |
| rs134041 (chr22:28056338)                                    | MN1          | T            | C                | 0.43               | -0.045 (0.008) | 4.19E-09 | 37669 | 0.092              |
| rs7050036 (chrX:15964845)                                    | AP1S2        | T            | A                | 0.38               | -0.014 (0.007) | 4.41E-02 | 32292 | 0.013              |
| Total r2 for new variants                                    |              |              |                  |                    |                |          |       | 0.758              |
| Total additive polygenic variance for new variants           |              |              |                  |                    |                |          |       | 1.896              |
| Total r <sup>2</sup> for known and new variants              |              |              |                  |                    |                |          |       | 1.614              |
| Total additive polygenic variance for known and new variants |              |              |                  |                    |                |          |       | 4.034              |

b. FEV<sub>1</sub>/FVC

| rs number (chr: position)                                   | Closest gene     | Coded allele | Non coded allele | Coded allele freq. | Beta (SE)      | P        | N     | r <sup>2</sup> (%) |
|-------------------------------------------------------------|------------------|--------------|------------------|--------------------|----------------|----------|-------|--------------------|
| <b>Known</b>                                                |                  |              |                  |                    |                |          |       |                    |
| rs2284746 (chr1:17306675)                                   | <i>MFAP2</i>     | C            | G                | 0.50               | 0.043 (0.008)  | 2.19E-08 | 36208 | 0.086              |
| rs993925 (chr1:218860068)                                   | <i>TGFB2</i>     | C            | T                | 0.66               | -0.021 (0.008) | 1.04E-02 | 35582 | 0.018              |
| rs1430193 (chr2:56120853)                                   | <i>EFEMP1</i>    | A            | T                | 0.61               | -0.012 (0.008) | 1.25E-01 | 35808 | 0.007              |
| rs2571445 (chr2:218683154)                                  | <i>TNS1</i>      | A            | G                | 0.40               | -0.012 (0.008) | 1.11E-01 | 37537 | 0.007              |
| rs12477314 (chr2:239877148)                                 | <i>HDAC4</i>     | C            | T                | 0.80               | -0.052 (0.009) | 3.59E-08 | 37915 | 0.080              |
| rs1529672 (chr3:25520582)                                   | <i>RARB</i>      | C            | A                | 0.83               | -0.046 (0.01)  | 6.43E-06 | 36292 | 0.056              |
| rs1344555 (chr3:169300219)                                  | <i>MECOM</i>     | C            | T                | 0.79               | 0.021 (0.01)   | 2.81E-02 | 35856 | 0.013              |
| rs2045517 (chr4:89870964)                                   | <i>FAM13A</i>    | C            | T                | 0.59               | 0.035 (0.008)  | 4.78E-06 | 38078 | 0.055              |
| rs10516526 (chr4:106688904)                                 | <i>GSTCD</i>     | A            | G                | 0.94               | -0.051 (0.016) | 1.08E-03 | 37267 | 0.029              |
| rs11100860 (chr4:145479139)                                 | <i>HHIP</i>      | A            | G                | 0.58               | -0.054 (0.008) | 8.60E-13 | 38046 | 0.134              |
| rs153916 (chr5:95036700)                                    | <i>SPATA9</i>    | C            | T                | 0.44               | 0.032 (0.008)  | 3.55E-05 | 37429 | 0.046              |
| rs1985524 (chr5:147847788)                                  | <i>HTR4</i>      | G            | C                | 0.54               | -0.039 (0.008) | 2.50E-07 | 37246 | 0.071              |
| rs11134779 (chr5:156936766)                                 | <i>ADAM19</i>    | A            | G                | 0.66               | 0.036 (0.008)  | 4.06E-06 | 38073 | 0.056              |
| rs6923462 (chr6:7801112)                                    | <i>BMP6</i>      | T            | C                | 0.84               | 0 (0.01)       | 9.92E-01 | 36987 | 0.000              |
| rs6903823 (chr6:28322296)                                   | <i>ZKSCAN3</i>   | A            | G                | 0.78               | 0.013 (0.01)   | 1.78E-01 | 37958 | 0.005              |
| rs114327456 (chr6:31568469)                                 | <i>NCR3</i>      | G            | A                | 0.78               | 0.023 (0.01)   | 2.08E-02 | 34980 | 0.015              |
| rs114177847 (chr6:32151443)                                 | <i>AGER</i>      | C            | T                | 0.95               | -0.118 (0.021) | 2.08E-08 | 25785 | 0.122              |
| rs2798641 (chr6:109268050)                                  | <i>ARMC2</i>     | C            | T                | 0.82               | 0.033 (0.01)   | 7.86E-04 | 37689 | 0.030              |
| rs262129 (chr6:142853144)                                   | <i>LOC153910</i> | A            | G                | 0.70               | -0.033 (0.008) | 5.92E-05 | 37568 | 0.043              |
| rs16909859 (chr9:98204792)                                  | <i>PTCH1</i>     | G            | A                | 0.92               | 0.055 (0.014)  | 1.43E-04 | 33738 | 0.043              |
| rs16909898 (chr9:98231008)                                  | <i>PTCH1</i>     | A            | G                | 0.90               | 0.052 (0.013)  | 5.48E-05 | 36153 | 0.045              |
| rs7068966 (chr10:12277992)                                  | <i>CDC123</i>    | C            | T                | 0.48               | -0.034 (0.008) | 6.00E-06 | 37816 | 0.054              |
| rs11001819 (chr10:78315224)                                 | <i>C10orf11</i>  | G            | A                | 0.52               | -0.018 (0.008) | 2.00E-02 | 38002 | 0.014              |
| rs4237643 (chr11:43648368)                                  | <i>HSD17B12</i>  | T            | G                | 0.30               | -0.004 (0.008) | 6.64E-01 | 38001 | 0.000              |
| rs2863171 (chr11:45250732)                                  | <i>PRDM11</i>    | A            | C                | 0.84               | -0.009 (0.01)  | 3.77E-01 | 38121 | 0.002              |
| rs11172113 (chr12:57527283)                                 | <i>LRP1</i>      | T            | C                | 0.60               | -0.032 (0.008) | 3.41E-05 | 37707 | 0.046              |
| rs1036429 (chr12:96271428)                                  | <i>CCDC38</i>    | T            | C                | 0.19               | 0.03 (0.01)    | 1.84E-03 | 38106 | 0.025              |
| rs8033889 (chr15:71680080)                                  | <i>THSD4</i>     | G            | T                | 0.78               | 0.071 (0.009)  | 4.31E-15 | 38063 | 0.162              |
| rs12447804 (chr16:58075282)                                 | <i>MMP15</i>     | C            | T                | 0.77               | 0.024 (0.009)  | 6.36E-03 | 37766 | 0.020              |
| rs2865531 (chr16:75390316)                                  | <i>CFDP1</i>     | T            | A                | 0.41               | 0.037 (0.008)  | 1.29E-06 | 37925 | 0.062              |
| rs1079572 (chr16:78187138)                                  | <i>WVOX</i>      | G            | A                | 0.43               | -0.002 (0.008) | 7.84E-01 | 37792 | 0.000              |
| rs6501431 (chr17:68976415)                                  | <i>KCNJ2</i>     | C            | T                | 0.21               | 0.014 (0.009)  | 1.24E-01 | 37852 | 0.006              |
| rs9978142 (chr21:35652239)                                  | <i>KCNE2</i>     | A            | T                | 0.85               | 0.028 (0.011)  | 7.58E-03 | 37623 | 0.019              |
| <b>Total r<sup>2</sup> for known variants</b>               |                  |              |                  |                    |                |          |       | 1.372              |
| <b>Total additive polygenic variance for known variants</b> |                  |              |                  |                    |                |          |       | 3.430              |
| <b>New</b>                                                  |                  |              |                  |                    |                |          |       |                    |
| rs6681426 (chr1:150586971)                                  | <i>ENSA</i>      | G            | A                | 0.36               | 0.014 (0.008)  | 7.47E-02 | 37927 | 0.008              |
| rs201204531 (chr1:219963090)                                | <i>RNU5F-1</i>   | A            | ATG              | 0.41               | -0.038 (0.008) | 1.98E-06 | 34866 | 0.065              |

| rs number (chr: position)                                    | Closest gene | Coded allele | Non coded allele | Coded allele freq. | Beta (SE)      | P        | N     | r <sup>2</sup> (%) |
|--------------------------------------------------------------|--------------|--------------|------------------|--------------------|----------------|----------|-------|--------------------|
| rs61067109 (chr2:18292452)                                   | KCNS3        | G            | A                | 0.77               | -0.05 (0.009)  | 3.09E-08 | 37416 | 0.082              |
| rs6441207 (chr3:158282459)                                   | AK097794     | C            | T                | 0.59               | -0.003 (0.008) | 6.56E-01 | 36408 | 0.001              |
| rs6856422 (chr4:106841962)                                   | NPNT         | G            | T                | 0.53               | -0.044 (0.008) | 1.30E-07 | 31446 | 0.089              |
| rs148274477 (chr6:142838173)                                 | LOC153910    | C            | T                | 0.98               | -0.161 (0.027) | 2.68E-09 | 30398 | 0.116              |
| rs34886460 (chr9:119359372)                                  | ASTN2        | T            | TA               | 0.53               | 0.041 (0.008)  | 6.75E-08 | 37567 | 0.078              |
| rs2274116 (chr9:139094805)                                   | LHX3         | C            | T                | 0.67               | -0.013 (0.009) | 1.29E-01 | 32205 | 0.007              |
| rs11383346 (chr12:28283187)                                  | CCDC91       | A            | AT               | 0.41               | -0.002 (0.008) | 8.38E-01 | 37497 | 0.000              |
| rs10850377 (chr12:115201436)                                 | TBX3         | G            | A                | 0.67               | -0.02 (0.008)  | 1.10E-02 | 37245 | 0.017              |
| rs7155279 (chr14:92485881)                                   | TRIP11       | G            | T                | 0.64               | -0.023 (0.008) | 3.49E-03 | 37675 | 0.023              |
| rs117068593 (chr14:93118229)                                 | RIN3         | C            | T                | 0.82               | 0.008 (0.01)   | 4.23E-01 | 34476 | 0.002              |
| rs12149828 (chr16:10706328)                                  | TEKT5        | G            | A                | 0.83               | 0.049 (0.01)   | 3.16E-06 | 33999 | 0.064              |
| rs113473882 (chr19:41124155)                                 | LTBP4        | T            | C                | 0.98               | -0.174 (0.033) | 1.48E-07 | 32207 | 0.086              |
| rs134041 (chr22:28056338)                                    | MN1          | T            | C                | 0.43               | -0.025 (0.008) | 1.06E-03 | 37653 | 0.028              |
| rs7050036 (chrX:15964845)                                    | AP1S2        | T            | A                | 0.38               | -0.041 (0.007) | 4.37E-09 | 32285 | 0.107              |
| Total r <sup>2</sup> for new variants                        |              |              |                  |                    |                |          |       | 0.772              |
| Total additive polygenic variance for new variants           |              |              |                  |                    |                |          |       | 1.931              |
| Total r <sup>2</sup> for known and new variants              |              |              |                  |                    |                |          |       | 2.144              |
| Total additive polygenic variance for known and new variants |              |              |                  |                    |                |          |       | 5.361              |

c. FVC

| rs number (chr: position)                                   | Closest gene     | Coded allele | Non coded allele | Coded allele freq. | Beta (SE)      | P        | N     | r <sup>2</sup> (%) |
|-------------------------------------------------------------|------------------|--------------|------------------|--------------------|----------------|----------|-------|--------------------|
| <b>Known</b>                                                |                  |              |                  |                    |                |          |       |                    |
| rs2284746 (chr1:17306675)                                   | <i>MFAP2</i>     | C            | G                | 0.50               | -0.039 (0.008) | 3.61E-07 | 35967 | 0.072              |
| rs993925 (chr1:218860068)                                   | <i>TGFB2</i>     | C            | T                | 0.66               | -0.006 (0.008) | 4.86E-01 | 35348 | 0.001              |
| rs1430193 (chr2:56120853)                                   | <i>EFEMP1</i>    | A            | T                | 0.61               | 0.032 (0.008)  | 9.67E-05 | 35571 | 0.043              |
| rs2571445 (chr2:218683154)                                  | <i>TNS1</i>      | A            | G                | 0.40               | -0.031 (0.008) | 6.97E-05 | 37297 | 0.042              |
| rs12477314 (chr2:239877148)                                 | <i>HDAC4</i>     | C            | T                | 0.80               | 0.002 (0.009)  | 8.15E-01 | 37678 | 0.000              |
| rs1529672 (chr3:25520582)                                   | <i>RARB</i>      | C            | A                | 0.83               | 0.003 (0.01)   | 7.58E-01 | 36053 | 0.000              |
| rs1344555 (chr3:169300219)                                  | <i>MECOM</i>     | C            | T                | 0.79               | 0.023 (0.01)   | 1.46E-02 | 35627 | 0.017              |
| rs2045517 (chr4:89870964)                                   | <i>FAM13A</i>    | C            | T                | 0.59               | -0.023 (0.008) | 2.66E-03 | 37839 | 0.024              |
| rs10516526 (chr4:106688904)                                 | <i>GSTCD</i>     | A            | G                | 0.94               | -0.076 (0.016) | 1.54E-06 | 37028 | 0.062              |
| rs11100860 (chr4:145479139)                                 | <i>HHIP</i>      | A            | G                | 0.58               | 0.009 (0.008)  | 2.30E-01 | 37807 | 0.004              |
| rs153916 (chr5:95036700)                                    | <i>SPATA9</i>    | C            | T                | 0.44               | -0.029 (0.008) | 1.62E-04 | 37195 | 0.038              |
| rs1985524 (chr5:147847788)                                  | <i>HTR4</i>      | G            | C                | 0.54               | -0.02 (0.008)  | 1.13E-02 | 37010 | 0.017              |
| rs11134779 (chr5:156936766)                                 | <i>ADAM19</i>    | A            | G                | 0.66               | 0.007 (0.008)  | 3.60E-01 | 37834 | 0.002              |
| rs6923462 (chr6:7801112)                                    | <i>BMP6</i>      | T            | C                | 0.84               | 0.048 (0.01)   | 3.52E-06 | 36750 | 0.059              |
| rs6903823 (chr6:28322296)                                   | <i>ZKSCAN3</i>   | A            | G                | 0.78               | 0.03 (0.01)    | 2.55E-03 | 37719 | 0.024              |
| rs114327456 (chr6:31568469)                                 | <i>NCR3</i>      | G            | A                | 0.78               | 0.025 (0.01)   | 1.47E-02 | 34741 | 0.017              |
| rs114177847 (chr6:32151443)                                 | <i>AGER</i>      | C            | T                | 0.95               | 0.048 (0.022)  | 2.79E-02 | 25540 | 0.019              |
| rs2798641 (chr6:109268050)                                  | <i>ARMC2</i>     | C            | T                | 0.82               | 0.007 (0.01)   | 4.81E-01 | 37450 | 0.001              |
| rs262129 (chr6:142853144)                                   | <i>LOC153910</i> | A            | G                | 0.70               | 0.005 (0.008)  | 5.48E-01 | 37330 | 0.001              |
| rs16909859 (chr9:98204792)                                  | <i>PTCH1</i>     | G            | A                | 0.92               | -0.048 (0.014) | 9.58E-04 | 33507 | 0.033              |
| rs16909898 (chr9:98231008)                                  | <i>PTCH1</i>     | A            | G                | 0.90               | -0.072 (0.013) | 2.87E-08 | 35924 | 0.086              |
| rs7068966 (chr10:12277992)                                  | <i>CDC123</i>    | C            | T                | 0.48               | -0.015 (0.008) | 5.33E-02 | 37577 | 0.010              |
| rs11001819 (chr10:78315224)                                 | <i>C10orf11</i>  | G            | A                | 0.52               | -0.016 (0.008) | 3.26E-02 | 37763 | 0.012              |
| rs4237643 (chr11:43648368)                                  | <i>HSD17B12</i>  | T            | G                | 0.30               | -0.028 (0.008) | 7.14E-04 | 37763 | 0.030              |
| rs2863171 (chr11:45250732)                                  | <i>PRDM11</i>    | A            | C                | 0.84               | -0.031 (0.01)  | 3.23E-03 | 37882 | 0.023              |
| rs11172113 (chr12:57527283)                                 | <i>LRP1</i>      | T            | C                | 0.60               | 0.013 (0.008)  | 8.95E-02 | 37468 | 0.008              |
| rs1036429 (chr12:96271428)                                  | <i>CCDC38</i>    | T            | C                | 0.19               | -0.006 (0.01)  | 5.48E-01 | 37867 | 0.001              |
| rs8033889 (chr15:71680080)                                  | <i>THSD4</i>     | G            | T                | 0.78               | -0.011 (0.009) | 2.25E-01 | 37824 | 0.004              |
| rs12447804 (chr16:58075282)                                 | <i>MMP15</i>     | C            | T                | 0.77               | -0.005 (0.009) | 6.06E-01 | 37525 | 0.001              |
| rs2865531 (chr16:75390316)                                  | <i>CFDP1</i>     | T            | A                | 0.41               | 0.004 (0.008)  | 6.11E-01 | 37685 | 0.001              |
| rs1079572 (chr16:78187138)                                  | <i>WVOX</i>      | G            | A                | 0.43               | 0.017 (0.008)  | 2.21E-02 | 37553 | 0.014              |
| rs6501431 (chr17:68976415)                                  | <i>KCNJ2</i>     | C            | T                | 0.21               | -0.033 (0.009) | 3.74E-04 | 37612 | 0.034              |
| rs9978142 (chr21:35652239)                                  | <i>KCNE2</i>     | A            | T                | 0.85               | -0.011 (0.011) | 2.81E-01 | 37382 | 0.003              |
| <b>Total r<sup>2</sup> for known variants</b>               |                  |              |                  |                    |                |          |       | 0.703              |
| <b>Total additive polygenic variance for known variants</b> |                  |              |                  |                    |                |          |       | 1.757              |
| <b>New</b>                                                  |                  |              |                  |                    |                |          |       |                    |
| rs6681426 (chr1:150586971)                                  | <i>ENSA</i>      | G            | A                | 0.36               | 0.036 (0.008)  | 4.74E-06 | 37688 | 0.056              |
| rs201204531 (chr1:219963090)                                | <i>RNU5F-1</i>   | A            | ATG              | 0.41               | 0.011 (0.008)  | 1.53E-01 | 34632 | 0.006              |

| rs number (chr: position)                                    | Closest gene | Coded allele | Non coded allele | Coded allele freq. | Beta (SE)      | P        | N     | r <sup>2</sup> (%) |
|--------------------------------------------------------------|--------------|--------------|------------------|--------------------|----------------|----------|-------|--------------------|
| rs61067109 (chr2:18292452)                                   | KCNS3        | G            | A                | 0.77               | -0.009 (0.009) | 3.05E-01 | 37177 | 0.003              |
| rs6441207 (chr3:158282459)                                   | AK097794     | C            | T                | 0.59               | 0.036 (0.008)  | 4.54E-06 | 36173 | 0.058              |
| rs6856422 (chr4:106841962)                                   | NPNT         | G            | T                | 0.53               | -0.02 (0.008)  | 1.54E-02 | 31226 | 0.019              |
| rs148274477 (chr6:142838173)                                 | LOC153910    | C            | T                | 0.98               | 0.114 (0.027)  | 3.07E-05 | 30110 | 0.058              |
| rs34886460 (chr9:119359372)                                  | ASTN2        | T            | TA               | 0.53               | 0 (0.008)      | 9.72E-01 | 37330 | 0.000              |
| rs2274116 (chr9:139094805)                                   | LHX3         | C            | T                | 0.67               | 0.041 (0.009)  | 2.68E-06 | 32004 | 0.069              |
| rs11383346 (chr12:28283187)                                  | CCDC91       | A            | AT               | 0.41               | -0.043 (0.008) | 3.83E-08 | 37254 | 0.081              |
| rs10850377 (chr12:115201436)                                 | TBX3         | G            | A                | 0.66               | -0.033 (0.008) | 3.60E-05 | 37015 | 0.046              |
| rs7155279 (chr14:92485881)                                   | TRIP11       | G            | T                | 0.64               | -0.031 (0.008) | 8.62E-05 | 37439 | 0.041              |
| rs117068593 (chr14:93118229)                                 | RIN3         | C            | T                | 0.82               | -0.054 (0.01)  | 1.74E-07 | 34254 | 0.080              |
| rs12149828 (chr16:10706328)                                  | TEKT5        | G            | A                | 0.83               | 0.005 (0.01)   | 6.12E-01 | 33774 | 0.001              |
| rs113473882 (chr19:41124155)                                 | LTBP4        | T            | C                | 0.98               | 0.073 (0.033)  | 2.88E-02 | 31982 | 0.015              |
| rs134041 (chr22:28056338)                                    | MN1          | T            | C                | 0.43               | -0.031 (0.008) | 5.44E-05 | 37415 | 0.044              |
| rs7050036 (chrX:15964845)                                    | AP1S2        | T            | A                | 0.38               | 0.01 (0.007)   | 1.47E-01 | 32283 | 0.007              |
| Total r <sup>2</sup> for new variants                        |              |              |                  |                    |                |          |       | 0.582              |
| Total additive polygenic variance for new variants           |              |              |                  |                    |                |          |       | 1.454              |
| Total r <sup>2</sup> for known and new variants              |              |              |                  |                    |                |          |       | 1.284              |
| Total additive polygenic variance for known and new variants |              |              |                  |                    |                |          |       | 3.211              |

**Supplementary Table 8** Results for 1000 Genomes sentinel variants with lower allele frequency than HapMap sentinel variants in two known loci

Shown are stage 1 and UK BiLEVE results for sentinel variants in previously reported lung function regions <sup>2-5</sup> which had minor allele frequency (<10%) more than two-fold lower than the HapMap sentinel variants in these regions, with the exception of a signal in *GPR126* (rs148274477) whose results are presented in **Table 1**. “GWAS sentinel” and “GWAS gene” present the sentinel SNP reported in a previous GWAS <sup>3</sup> and the closest gene to sentinel SNP respectively. Chr., chromosome.

| GWAS sentinel | GWAS gene    | rs number (chr:position)     | R2 with sentinel | Coded/ other allele | Stage 1 |       |        |       |          | UK BiLEVE |       |        |       |          |
|---------------|--------------|------------------------------|------------------|---------------------|---------|-------|--------|-------|----------|-----------|-------|--------|-------|----------|
|               |              |                              |                  |                     | MAF     | Neff  | Beta   | SE    | P        | MAF       | Neff  | Beta   | SE    | P        |
| rs993925      | <i>TGFB2</i> | rs147187942 (chr1:218773216) | 1.73E-02         | T/A                 | 0.090   | 31881 | -0.047 | 0.014 | 8.72E-04 | 0.085     | 46263 | -0.032 | 0.012 | 5.72E-03 |
| rs12447804    | <i>MMP15</i> | rs150232756 (chr16:57691218) | 9.78E-06         | C/T                 | 0.005   | 28940 | 0.203  | 0.057 | 3.65E-04 | 0.005     | 42760 | -0.057 | 0.051 | 2.67E-01 |

### Supplementary Table 9 MAGENTA results

MAGENTA results both for the main analysis (“main”) and the sensitivity analysis after removing the HLA region (“sensitivity (no HLA)”) for pathways that met a Bonferroni threshold corrected for the number of pathways tested per database and had an FDR<5% in the main analysis are presented.

| Measure | Analysis             | Database                   | Bonferroni corrected threshold | Pathway                            | P        | FDR    |
|---------|----------------------|----------------------------|--------------------------------|------------------------------------|----------|--------|
| FVC     | main                 | Ingenuity                  | 6.17E-04                       | PDGF.Signaling                     | 2.00E-04 | 0.0028 |
| FVC     | main                 | PANTHER BIOLOGICAL PROCESS | 2.30E-04                       | Chromatin packaging and remodeling | 1.82E-04 | 0.0357 |
| FVC     | sensitivity (no HLA) | Ingenuity                  | 6.17E-04                       | PDGF Signaling                     | 6.60E-05 | 0.0023 |
| FVC     | sensitivity (no HLA) | PANTHER BIOLOGICAL PROCESS | 2.30E-04                       | Chromatin packaging and remodeling | 4.00E-04 | 0.0781 |

## Supplementary Notes:

### Supplementary Note 1: Heterogeneity test

A Chi-square test for heterogeneity was undertaken and  $I^2$  calculated for the stage 1 results across studies for the 16 novel sentinel variants. Results are presented below; none of the results meets a Bonferroni corrected threshold for 16 tests ( $P < 3.13 \times 10^{-3}$ ).

| rs number (chr:position)        | Gene (function)                                           | Measure               | $\chi^2$ | P        | Degrees of freedom | $I^2$ |
|---------------------------------|-----------------------------------------------------------|-----------------------|----------|----------|--------------------|-------|
| rs6681426<br>(chr1:150586971)   | <i>MCL1</i> (dist=34757), <i>ENSA</i> (dist=7628)         | FEV <sub>1</sub>      | 12.37    | 7.18E-01 | 16                 | 0.00  |
| rs201204531<br>(chr1:219963090) | <i>LYPLAL1</i> (dist=576883), <i>RNU5F-1</i> (dist=83529) | FEV <sub>1</sub> /FVC | 12.51    | 5.65E-01 | 14                 | 0.00  |
| rs61067109<br>(chr2:18292452)   | <i>KCNS3</i> (dist=178227), <i>NT5C1B</i> (dist=443537)   | FEV <sub>1</sub> /FVC | 17.30    | 3.66E-01 | 16                 | 7.54  |
| rs6441207<br>(chr3:158282459)   | <i>AK097794</i> (ncRNA_intronic)                          | FVC                   | 11.69    | 7.02E-01 | 15                 | 0.00  |
| rs6856422<br>(chr4:106841962)   | <i>NPNT</i> (intronic)                                    | FEV <sub>1</sub> /FVC | 9.62     | 8.43E-01 | 15                 | 0.00  |
| rs148274477<br>(chr6:142838173) | <i>GPR126</i> (dist=70770), <i>LOC153910</i> (dist=9419)  | FEV <sub>1</sub> /FVC | 25.12    | 6.77E-02 | 16                 | 36.31 |
| rs34886460<br>(chr9:119359372)  | <i>ASTN2</i> (intronic)                                   | FEV <sub>1</sub> /FVC | 9.20     | 9.05E-01 | 16                 | 0.00  |
| rs2274116<br>(chr9:139094805)   | <i>LHX3</i> (exonic)                                      | FVC                   | 25.52    | 4.34E-02 | 15                 | 41.22 |
| rs11383346<br>(chr12:28283187)  | <i>PTHLH</i> (dist=158271), <i>CCDC91</i> (dist=126946)   | FVC                   | 18.35    | 3.04E-01 | 16                 | 12.82 |
| rs10850377<br>(chr12:115201436) | <i>TBX3</i> (dist=79467), <i>MED13L</i> (dist=1194945)    | FEV <sub>1</sub>      | 25.10    | 6.81E-02 | 16                 | 36.26 |
| rs7155279<br>(chr14:92485881)   | <i>TRIP11</i> (intronic)                                  | FEV <sub>1</sub>      | 12.43    | 7.14E-01 | 16                 | 0.00  |
| rs117068593<br>(chr14:93118229) | <i>RIN3</i> (exonic)                                      | FEV <sub>1</sub>      | 16.86    | 3.27E-01 | 15                 | 11.02 |
| rs12149828<br>(chr16:10706328)  | <i>EMP2</i> (dist=31789), <i>TEKT5</i> (dist=15033)       | FEV <sub>1</sub> /FVC | 19.17    | 2.06E-01 | 15                 | 21.75 |
| rs113473882<br>(chr19:41124155) | <i>LTBP4</i> (intronic)                                   | FEV <sub>1</sub> /FVC | 15.91    | 4.59E-01 | 16                 | 0.00  |
| rs134041<br>(chr22:28056338)    | <i>MIAT</i> (dist=983898), <i>MN1</i> (dist=87927)        | FEV <sub>1</sub>      | 13.89    | 6.07E-01 | 16                 | 0.00  |
| rs7050036<br>(chrX:15964845)    | <i>AP1S2</i> (dist=91708), <i>GRPR</i> (dist=176579)      | FF                    | 9.49     | 7.35E-01 | 13                 | 0.00  |

## Supplementary Note 2: Stepwise conditional analysis to identify multiple signals within each region

In order to identify independent signals within regions already associated with lung function, we undertook a stepwise conditional analysis using GCTA<sup>20</sup> for each of the previously discovered<sup>1-5</sup> and new regions. This method uses a stepwise procedure to select a subset of independent variants that when fitted together in the model each has a joint  $P$  value below a pre specified threshold. In order to be comprehensive we defined the threshold for inclusion in the model as joint  $P$  value  $< 10^{-3}$  and we defined regions as 1Mb either side of the sentinel variant; when two regions overlapped we merged them into one larger region.

We identified one additional independent ( $r^2 < 0.02$  with sentinel variant) variant with joint  $P$  value  $< 10^{-5}$  in two regions, near the previously discovered signals in *ZKSCAN3* and *CCDC38* (see bold  $P$ -values in the table below). Models including the variants selected by the stepwise conditional analysis in these two regions were fitted using UK BiLEVE data and none of these two variants was significant.

| Known sentinel<br>rs number<br>(chr:position) | Known<br>GWAS<br>gene<br>symbol | rs number<br>(chr:position)     | Code<br>d<br>allele<br>/<br>other<br>allele | R <sup>2</sup> with<br>sentinel | Dataset   | Unconditional results        |        |       |          | Joint analysis |       |                 | Correlation<br>(r) with the<br>next<br>variant |
|-----------------------------------------------|---------------------------------|---------------------------------|---------------------------------------------|---------------------------------|-----------|------------------------------|--------|-------|----------|----------------|-------|-----------------|------------------------------------------------|
|                                               |                                 |                                 |                                             |                                 |           | Coded<br>allele<br>frequency | Beta   | SE    | P        | Beta           | SE    | P               |                                                |
| rs6903823<br>(chr6:28322296)                  | ZKSCAN3                         | rs73395396<br>(chr6:27479793)   | C/T                                         | 0.02                            | stage 1   | 0.99                         | -0.046 | 0.045 | 3.13E-01 | 0.389          | 0.107 | 2.76E-04        | 0.92                                           |
|                                               |                                 |                                 |                                             |                                 | UK BiLEVE | 0.99                         | 0.055  | 0.032 | 8.78E-02 | 0.090          | 0.089 | 3.10E-01        | 0.93                                           |
|                                               |                                 | rs200955<br>(chr6:27839312)     | T/C                                         | 0.02                            | stage 1   | 0.99                         | -0.123 | 0.042 | 3.68E-03 | -0.477         | 0.100 | <b>2.00E-06</b> | 0.14                                           |
|                                               |                                 |                                 |                                             |                                 | UK BiLEVE | 0.99                         | -0.044 | 0.032 | 1.75E-01 | -0.065         | 0.090 | 4.67E-01        | 0.14                                           |
|                                               |                                 | rs1778483<br>(chr6:28240991)    | T/G                                         | 0.66                            | stage 1   | 0.73                         | 0.034  | 0.009 | 2.25E-04 | 0.036          | 0.009 | 8.64E-05        |                                                |
|                                               |                                 |                                 |                                             |                                 | UK BiLEVE | 0.68                         | 0.037  | 0.007 | 6.71E-08 | 0.036          | 0.007 | 1.84E-07        |                                                |
| rs1036429<br>(chr12:96271428)                 | CCDC38                          | rs200233711<br>(chr12:95306163) | T/TG                                        | 0.00                            | stage 1   | 0.60                         | 0.033  | 0.009 | 1.23E-04 | 0.038          | 0.009 | <b>9.20E-06</b> | -0.05                                          |
|                                               |                                 |                                 |                                             |                                 | UK BiLEVE | 0.59                         | 0.013  | 0.007 | 5.37E-02 | 0.013          | 0.007 | 5.63E-02        | -0.04                                          |
|                                               |                                 | rs66498225<br>(chr12:95330172)  | C/T                                         | 0.00                            | stage 1   | 0.94                         | -0.052 | 0.016 | 9.66E-04 | -0.056         | 0.016 | 4.11E-04        | -0.06                                          |
|                                               |                                 |                                 |                                             |                                 | UK BiLEVE | 0.93                         | -0.036 | 0.013 | 4.54E-03 | -0.036         | 0.013 | 5.20E-03        | -0.07                                          |
|                                               |                                 | rs2060304<br>(chr12:95486073)   | A/G                                         | 0.00                            | stage 1   | 0.94                         | -0.049 | 0.016 | 1.58E-03 | -0.065         | 0.016 | 4.12E-05        | 0.01                                           |
|                                               |                                 |                                 |                                             |                                 | UK BiLEVE | 0.93                         | 0.000  | 0.013 | 9.69E-01 | -0.007         | 0.013 | 6.08E-01        | 0.00                                           |
|                                               |                                 | rs150198783<br>(chr12:96141778) | G/A                                         | 0.00                            | stage 1   | 0.99                         | 0.154  | 0.037 | 3.11E-05 | 0.155          | 0.037 | 2.57E-05        | 0.02                                           |
|                                               |                                 |                                 |                                             |                                 | UK BiLEVE | 0.99                         | 0.020  | 0.043 | 6.38E-01 | 0.015          | 0.043 | 7.19E-01        | 0.05                                           |
|                                               |                                 | rs7134025<br>(chr12:96153846)   | C/T                                         | 0.25                            | stage 1   | 0.15                         | 0.045  | 0.011 | 2.43E-05 | 0.046          | 0.011 | 1.38E-05        | 0.01                                           |
|                                               |                                 |                                 |                                             |                                 | UK BiLEVE | 0.14                         | 0.023  | 0.009 | 1.60E-02 | 0.023          | 0.009 | 1.47E-02        | 0.03                                           |
|                                               |                                 | rs7959665<br>(chr12:97069873)   | G/A                                         | 0.00                            | stage 1   | 0.02                         | -0.096 | 0.028 | 6.89E-04 | -0.103         | 0.028 | 2.71E-04        |                                                |
|                                               |                                 |                                 |                                             |                                 | UK BiLEVE | 0.02                         | -0.026 | 0.023 | 2.45E-01 | -0.028         | 0.023 | 2.13E-01        |                                                |

## Supplementary Note 3: Individual study descriptions

### GWAS samples and phenotype measurement

This section describes study-specific characteristics that are not presented in the tables. All participants provided written informed consent and studies were approved by local Research Ethics Committees and/or Institutional Review boards.

Details of the **British 1958 Birth Cohort** biomedical follow-up have been previously reported<sup>117</sup>. Spirometry at age 44–45 years was done in the standing position without nose clips, using a Vitalograph handheld spirometer as previously described<sup>118</sup>. In the analysis, all readings with a best-test variation greater than 10% were excluded.

The **Busselton Health Study** (BHS) is a longitudinal survey of the town of Busselton in the southwestern region of Western Australia that began in 1966. In 1994/1995 a cross-sectional community follow-up study was undertaken where blood was taken for DNA extraction. A sample of 1,168 European-ancestry individuals were genotyped using the Illumina 610-Quad BeadChip (BHS1), and subsequent genotyping was carried out on an independent group of 3,428 European-ancestry individuals using Illumina 660W-Quad (BHS2). Spirometric measures of forced expired volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) were assessed.

The CROATIA study was initiated to investigate the use of isolated rather than urban populations for the identification of genes associated with medically-relevant quantitative traits. Three cohorts have been recruited as part of the CROATIA study: **CROATIA-Vis**<sup>119</sup>, **CROATIA-Korcula**<sup>120</sup> and

**CROATIA-Split**<sup>121</sup>. CROATIA-Vis was the first to be collected when 1,008 Croatians aged 18-93 recruited from the villages of Komiza and Vis on the Dalmatian island of Vis. Recruitment occurred from 2003 to 2004 with participants donating blood for DNA extraction and biochemical measurements as well as undergoing some anthropometric measurements and physiological tests to measure traits such as height, weight and blood pressure, and finally completing several questionnaires relating to general health, medical history, diet and lifestyle. CROATIA-Korcula was recruited from 2007 to 2008 from the town of Korcula and the villages of Lumbarda, Zrnovo and Racisce on the island of Korcula, Croatia with 969 adults aged 18-98 agreeing to participate. This study followed the same recruitment procedures as CROATIA-Vis and the same samples and tests were collected with a few additions to reflect the research interests and expertise in Edinburgh. Volunteers were recruited to be part of the CROATIA-Split cohort in 2009-2010 from the Dalmatian mainland city of Split. This is the main ferry port to the islands and is the second largest city in Croatia and the largest along the Dalmatian coast. 1,012 adults aged 18-85 were recruited using the same methodology and with the same samples collected as in CROATIA-Korcula. Ethical approval was obtained from appropriate regulatory bodies in both Scotland and Croatia and participants gave informed consent prior to joining the study.

The **EPIC Norfolk** GWA cohort includes 2,566 participants randomly selected from the EPIC-Norfolk Study, a population-based cohort study of 25,663 men and women of European descent aged 39-79 years recruited in Norfolk, UK between 1993 and 1997<sup>122</sup>. Respiratory function was assessed by spirometry<sup>123,124</sup>. Forced expiratory volume in 1 second ( $FEV_1$ ) and forced vital capacity (FVC) were measured twice using a portable spirometer (Micro Medical, Rochester, United Kingdom). The higher values of the two readings for  $FEV_1$  and FVC were used for the analyses.

The **Generation Scotland: Scottish Family Health Study** is a collaboration between the Scottish Universities and the NHS, funded by the Chief Scientist Office of the Scottish Government. GS:SFHS is a family-based genetic epidemiology cohort with DNA, other biological samples (serum, urine and cryopreserved whole blood) and socio-demographic and clinical data from ~24,000 volunteers, aged 18-98 years, in ~7,000 family groups. Participants were recruited across Scotland, with some family members from further afield, from 2006-2011. Most (87%) participants were born in Scotland and 96% in the UK or Ireland. The cohort profile has been published<sup>125</sup>. GS:SFHS operates under appropriate ethical approvals, and all participants gave written informed consent. Generation Scotland is a collaboration between the University Medical Schools and National Health Service in Aberdeen, Dundee, Edinburgh and Glasgow (UK).

The DNA archive established from the **Health 2000** Survey Cohort was used. Details of this study population and phenotyping procedures have been previously reported<sup>126</sup>. Genome-wide genotyping was available for 2124 individuals selected from the Health 2000 cohort as metabolic syndrome cases and their matched controls<sup>127</sup>. Spirometry was done in the standing position without nose clips, using a Vitalograph 2150 spirometer. In the analysis, the maximum permissible difference between the two highest FEV<sub>1</sub> and FVC values was 10%.

The KORA studies (Cooperative Health Research in the Region of Augsburg) are a series of independent population based studies from the general population living in the region of Augsburg, Southern Germany<sup>128,129</sup>. **KORA F4** including 3,080 individuals was conducted from 2006-2008 as a follow-up study to KORA S4 (1999-2001). Lung function tests were performed in a random subsample of subjects born between 1946 and 1965 (age range 41–63 years). Spirometry was performed in line with the ATS/ERS recommendations<sup>130</sup> using a pneumotachograph-type spirometer

(Masterscreen PC, CardinalHealth, Würzburg, Germany) before and after inhalation of 200µg salbutamol. The present study is based on maximum values of FEV<sub>1</sub> and FVC measured before bronchodilation. The spirometer was calibrated daily using a calibration pump (CardinalHealth, Würzburg, Germany), and additionally, an internal control was used to ensure constant instrumental conditions. For KORA F4 participants without spirometry measurements in 2006-2008, we used measurements from the KORA-Age time point conducted in 2008/09. KORA Age contains subjects from all KORA studies born until 1943 (aged 65-90 years)<sup>131</sup>. Spirometry was measured in 935 randomly selected participants. Conditions including the examiner were the same as in 2008/09 except that inhalation of salbutamol was not performed due to the high number of contraindications anticipated in this aged population.

The KORA studies (Cooperative Health Research in the Region of Augsburg) are a series of independent population based studies from the general population living in the region of Augsburg, Southern Germany<sup>128,129</sup>. The **KORA S3** study including 4,856 individuals was conducted in 1994/95. Spirometry was measured during a follow up in 1997/98 for all participants younger than 60 years who did not smoke or use inhalers one hour before the test. All spirometric tests were performed strictly adhering to the ECRHS protocol<sup>132,133</sup> using Biomedin Spirometers (Biomedin srl, Padova, Italy). Tests were accounted valid if at least two technically satisfactory manoeuvres could be obtained throughout a maximum of nine trials. FEV<sub>1</sub> and FVC were defined as the maximum value within all valid manoeuvres. For KORA S3 participants without spirometry measurements in 1997/98 we used measurements from the KORA-Age time point conducted in 2008/09. KORA Age contains subjects from all KORA studies born until 1943 (aged 65–90 years)<sup>131</sup>. Spirometry was measured in 935 randomly selected participants. Conditions including the examiner were the same as in KORA F4

(see below) except that inhalation of salbutamol was not performed due to the high number of contraindications anticipated in this aged population.

The **Lothian Birth Cohort 1936** consists of 1,091 relatively healthy individuals assessed on cognitive and medical traits at about 70 years of age. They were all born in 1936 and most took part in the Scottish Mental Survey of 1947. At baseline the sample of 548 men and 543 women had a mean age 69.6 years (s.d. = 0.8). They were all Caucasian, community-dwelling, and almost all lived in the Lothian region (Edinburgh city and surrounding area) of Scotland. A full description of participant recruitment and testing can be found elsewhere<sup>134</sup>. Genotyping was performed at the Wellcome Trust Clinical Research Facility, Edinburgh. Quality control measures were applied and 1,005 participants remained. Lung function assessing peak expiratory flow rate, forced expiratory volume in 1 second, and forced vital capacity (each the best of three), using a Micro Medical Spirometer was assessed, sitting down without nose clips, at age 70 years. The accuracy of the spirometer is  $\pm 3\%$  (to ATS recommendations Standardisation of Spirometry 1994 update for flows and volumes).

The **Northern Finland Birth Cohort** (NFBC) study programme was initiated in the 1960s. The cohort of women and their offspring was established in the provinces of Oulu and Lapland and had an expected date of birth in 1966 comprising 12,231 children (NFBC1966, 15). The NFBC1966 had spirometry and other measurements done at the age of 31 years. In NFBC1966, we used a Vitalograph P-model spirometer (Vitalograph Ltd., Buckingham, UK), with a volumetric accuracy of  $\pm 2\%$  or  $\pm 50$  mL whichever was greater. The spirometer was calibrated regularly using a 1-Litre precision syringe. The spirometric manoeuvre was performed three times but was repeated if the coefficient of variation between two maximal readings was  $>4\%$ .

The **Northern Sweden Population Health Study** (NSPHS) represents a cross-sectional study conducted in the communities of Karesuando (samples gathered in 2006) and Soppero (2009) in the subarctic region of the County of Norrbotten, Sweden. Spirometry was performed in sitting position without noseclips using a MicroMedicalSpida 5 spirometer (<http://www.medisave.co.uk>). Three consecutive 28 lung function measurements per participant were done and the maximum value per measured lung function parameter was used for further analysis. Relatedness was taken into account by applying the "polygenic" linear mixed effects model. Genome-wide association analysis was performed using a score test, a family-based association test<sup>135</sup> which uses the residuals and the variance-covariance matrix from the polygenic model and the SNP fixed effect coded under an additive model.

The **Orkney Complex Disease Study** (ORCADES) is an ongoing family-based, cross-sectional study in the isolated Scottish archipelago of Orkney. Spirometry was performed in the sitting position without nose clips, using a Spida handheld spirometer. Measurements were repeated once and the better reading was used for analysis.

The **SAPALDIA** cohort is a population-based multi-center study in eight geographic areas representing the range of environmental, meteorological and socio-demographic conditions in Switzerland<sup>136,137</sup>. It was initiated in 1991 (SAPALDIA 1) with a follow-up assessment in 2002 (SAPALDIA 2) and 2010 (SAPALDIA3). This study has specifically been designed to investigate longitudinally lung function, respiratory and cardiovascular health; to study and identify the

associations of these health indicators with individual long term exposure to air pollution, other toxic inhalants, life style and molecular factors.

The **Study of Health in West Pomerania** (SHIP) is a cross-sectional, population based survey in a region in the Northeast of Germany. Study details are given elsewhere<sup>138,139</sup>. The examinations were conducted using a bodyplethysmograph equipped with a pneumotachograph (VIASYS Healthcare, JAEGER, Hoechberg, Germany) which meets the American Thoracic Society (ATS) criteria<sup>140</sup>. The volume signal of the equipment was calibrated with a 3.0 litre syringe connected to the pneumotachograph in accordance with the manufacturer's recommendations and at least once on each day's testing. Barometric pressure, temperature and relative humidity were registered every morning. Calibration of reference gas and volume was examined under ATS-conditions (Ambient Temperature Pressure) and the integrated volumes were BTPS (Body Temperature Pressure Saturated) corrected<sup>140,141</sup>. Lung function variables were measured continuously throughout the baseline breathing and the forced manoeuvres using a VIASYS HEALTHCARE system (MasterScreen Body/Diff.). Spirometry flow volume loops were conducted in accordance with ATS recommendations 40 in a sitting position and with wearing noseclips. The participants performed at least three forced expiratory lung function manoeuvres in order to obtain a minimum of two acceptable and reproducible values 41. Immediate on-screen error codes indicating the major acceptability (including start, duration and end of test) and reproducibility criteria supported the attempt for standardised procedures. The procedure was continuously monitored by a physician. The best results for FVC, FEV<sub>1</sub>, peak expiratory flow (PEF) and expiratory flow at 75%, 50%, 25% of FVC (MEF 75, MEF 50, MEF 25) were taken. The ratio of FEV<sub>1</sub> to FVC was calculated from the largest FEV<sub>1</sub> and FVC.

The **YFS** is a population-based follow up-study started in 1980<sup>142</sup>. The main aim of the YFS is to determine the contribution made by childhood lifestyle, biological and psychological measures to the risk of cardiovascular diseases in adulthood. In 1980, over 3,500 children and adolescents all around Finland participated in the baseline study. The follow-up studies have been conducted mainly with 3-year intervals. The latest 30-year follow-up study was conducted in 2010-2011 (ages 33-49 years) with 2,063 participants. The study was approved by the local ethics committees (University Hospitals of Helsinki, Turku, Tampere, Kuopio and Oulu) and was conducted following the guidelines of the Declaration of Helsinki. All participants gave their written informed consent.

### **Follow-up samples and phenotype measurement**

The **Avon Longitudinal Study of Parents and their Children** (ALSPAC) is a population-based birth cohort study consisting initially of over 13,000 women and their children recruited in the county of Avon, UK in the early 1990s<sup>143</sup>. At 8–9 years of age, children's lung function was measured by spirometry (Vitalograph 2120, Maids Moreton, UK) according to American Thoracic Society criteria. Flow-volume curves were reviewed by a respiratory physician to ensure adherence to standards. GWA data and lung function measurements were available on 5,062 of the children from this study. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary>).

Details of the methods of **ECRHS I** and **ECRHS II**, a multicentre international cohort study, have been published elsewhere<sup>132,144</sup>. Participants within the ECRHS were eligible for inclusion in this analysis if

they were identified by random sampling of those who fulfilled the following criteria 1) lived in centres that took part in genome-wide genotyping initiative under the auspices of GABRIEL<sup>145</sup> AND 2) were initially selected to take part in the ECRHS clinical measurements as part of the random sample (ie not specifically selected for inclusion because of any pre-existing disease). Participants were included in this analysis if they also provided a technically satisfactory forced expiratory manoeuvre, compliant with ATS spirometry criteria, at the time of the first survey (aged 20-48). Most centers used the BIOMEDIN water-sealed spirometer for lung function measures and all centers conducted manoeuvres in the sitting position with nose clips on. Further details are available in<sup>146</sup>.

The **Prospective Investigation of the Vasculature in Uppsala Seniors** (PIVUS)<sup>147</sup> is a population-based study of the cardiovascular health in the elderly. The main purpose of PIVUS was to investigate the role The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) of endothelial function in cardiovascular risk. Mailed invitations were sent to subjects who lived in Uppsala, Sweden, within 2 months after their 70th birthday. The subjects were randomly selected from the community register. A total of 1,016 men and women participated in the baseline investigation (participation rate, 50.1%). Spirometry was performed in 901 subjects at baseline in accordance with American Thoracic Society recommendations ( $\alpha$  spirometer; Vitalograph Ltd; Buckingham, UK). The best value from three recordings was used. The Ethics Committee of the University of Uppsala approved the study, and the participants gave their informed consent. Genotyping of all samples was undertaken using the Illumina Omni Express and CardioMetaboChip. Genotypes were called using GENCALL. A total of 738,879 SNPs passed quality control (thresholds: call rate  $< 0.95$ , and call rate  $< 0.99$  for  $MAF < 5\%$ ;  $HWE P < 10^{-6}$ ). SNPs with  $MAF < 1\%$  were removed from the imputation scaffold. Imputation was performed using IMPUTE up to CEU haplotypes from Phase II HapMap reference panel.

For this analysis, 3,023 participants (85% female and all of Caucasian ancestry) within the **TwinsUK** adult twin registry based at St. Thomas' Hospital in London were analyzed for whom both genotype and IOP information was available. Twins largely volunteered unaware of the eye studies interests at the time of enrolment and gave fully informed consent under a protocol reviewed by the St. Thomas' Hospital Local Research Ethics Committee. Subjects were genotyped in two different batches of approximately the same size, using two genotyping platforms from Illumina: 300K Duo for and HumanHap610-Quad arrays. Whole genome imputation of the genotypes was performed using HapMap2 ([www.hapmap.org](http://www.hapmap.org)) haplotypes. Stringent quality control (QC) measures were implemented, including minimum genotyping success rate (>95%), Hardy-Weinberg equilibrium ( $P > 10^{-6}$ ), minimum MAF (>1%) and imputation quality score (>0.7). Subjects of non Caucasian ancestry were excluded from the analysis. Association was calculated for all SNPs using a score test as implemented in the software GEMMA<sup>148</sup> (<http://www.xzlab.org/software/gemma-0.94.tar.gz>), accounting for possible covariates as explained in the sections explaining the general methodology.

The **UK Biobank Lung Exome Variant Evaluation** (UK BiLEVE) project was the first genetic study in UK Biobank and is described in<sup>149</sup>. UK Biobank (<http://www.ukbiobank.ac.uk/>) contains data from 502,682 individuals (94% of self-reported European ancestry) with extensive health and life-style questionnaire data, physical measures (including spirometry) and DNA. Spirometry was undertaken using a Vitalograph Pneumotrac 6800. The participant was asked to record two to three blows (lasting for at least 6 seconds) within a period of about 6 minutes. The computer compared the reproducibility of the first two blows and, if acceptable (defined as a <5% difference in forced volume vital capacity (FVC) and Forced Expiratory Volume in 1 second (FEV<sub>1</sub>), a third blow was not required. For the UK BiLEVE project, a sampling frame of 275,939 individuals was defined as those who were of European

ancestry and had spirometry measures which met ERS/ATS guidelines<sup>130</sup>. A total of 50,008 samples were selected from the extremes and middle of the distributions of percent predicted FEV<sub>1</sub>, separately in never smokers and heavy smokers (20,005 individuals with low FEV<sub>1</sub>, 19,997 with average FEV<sub>1</sub> and 10,006 with high FEV<sub>1</sub>). DNA was extracted and genotyped with the custom-designed Affymetrix Axiom UK BiLEVE array. Following thorough variant and sample QC, 48,943 unrelated individuals remained for further analysis.

## **Supplementary Note 4: Investigators, contributions, funding and acknowledgments per study**

### ***SpiroMeta consortium***

**Analysis group:** Ian P Hall (co-chair), Suzanne Miller, Nick Shrine, María Soler Artigas, David P Strachan, Martin D Tobin (co-chair), Louise V Wain.

**Bioinformatics and functional assessment group:** Ian P Hall, Abdul K Kheirallah, Erik Melén, Suzanne Miller, Ioanna Ntalla, Ian Sayers, María Soler Artigas, Martin D Tobin, Louise V Wain.

**Writing group:** Ian P Hall (co-chair), Suzanne Miller, María Soler Artigas, David P Strachan, Martin D Tobin (co-chair), Louise V Wain.

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### ***GWAS studies***

#### **B58C**

**Investigators:** Wendy L McArdle, David P Strachan.

**Contributions:** project conception, design and management: D.P.S., phenotype collection and data management: W.L.M., D.P.S., data analysis: D.P.S. **Funding & Acknowledgements:** We acknowledge use of phenotype and genotype data from the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02. (<http://www.b58cgene.sgul.ac.uk/>). Genotyping for the B58C-WTCCC subset was funded by the Wellcome Trust grant 076113/B/04/Z. The B58C-T1DGC genotyping utilized resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human Development (NICHD), and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. B58C-T1DGC GWAS data were deposited by the Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research (CIMR), University of Cambridge, which is funded by Juvenile Diabetes Research Foundation International, the Wellcome Trust and the National Institute for Health Research Cambridge Biomedical Research Centre; the CIMR is in receipt of a Wellcome Trust Strategic Award (079895).

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## **BHS1&2**

**Investigators:** John Beilby, Jennie Hui, Alan L James, AW Musk.

**Contributions:** phenotype collection and data management: J.B., J. Hui, A.L.J, A.W.M. **Funding &**

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## **CROATIA-Korcula**

**Investigators:** Caroline Hayward, Jennifer E Huffman, Pau Navarro.

**Contributions:** project conception, design and management: C.H., phenotype collection and data management: C.H., J.E.H., P.N., data analysis: J.E.H., P.N. **Funding & Acknowledgements:** The CROATIA study was supported through grants from the Medical Research Council UK, the Ministry of Science, Education and Sport in the Republic of Croatia (number 216-1080315-0302), Croatian Science Foundation (grant 8875) and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). SNP genotyping for CROATIA-Vis was performed by the Wellcome Trust Clinical Research Facility (WTCRF) at the Western General Hospital, Edinburgh, UK. CROATIA-Korcula was genotyped by Helmholtz Zentrum München, GmbH, Neuherberg, Germany and CROATIA-Split by AROS Applied Biotechnology, Aarhus, Denmark. We would like to acknowledge the invaluable contributions of the recruitment teams in Croatia (including those from the Institute of Anthropological Research in Zagreb and the Croatian Centre for Global Health at the University of Split), the administrative teams in Croatia and Edinburgh and the people of Korcula, Vis and Split.

## **CROATIA-Split**

**Investigators:** Ivana Kolcic, Ozren Polasek, Veronique Vitart, Tatijana Zemunik.

**Contributions:** project conception, design and management: I.K., O.P., V.V., T.Z., phenotype collection and data management: I.K., O.P., V.V., T.Z., **Funding & Acknowledgements:** The CROATIA study was supported through grants from the Medical Research Council UK, the Ministry of Science, Education and Sport in the Republic of Croatia (number 216-1080315-0302), Croatian Science Foundation (grant 8875) and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). SNP genotyping for CROATIA-Vis was performed by the Wellcome Trust Clinical Research Facility (WTCRF) at the Western General Hospital, Edinburgh, UK. CROATIA-Korcula was genotyped by Helmholtz Zentrum München, GmbH, Neuherberg, Germany

and CROATIA-Split by AROS Applied Biotechnology, Aarhus, Denmark. We would like to acknowledge the invaluable contributions of the recruitment teams in Croatia (including those from the Institute of Anthropological Research in Zagreb and the Croatian Centre for Global Health at the University of Split), the administrative teams in Croatia and Edinburgh and the people of Korcula, Vis and Split.

## **CROATIA-Vis**

**Investigators:** Jonathan Marten, Igor Rudan, Alan F Wright.

**Contributions:** project conception, design and management: I.R., A.F.W., phenotype collection and data management: J.M., data analysis: J.M. **Funding & Acknowledgements:** The CROATIA study was supported through grants from the Medical Research Council UK, the Ministry of Science, Education and Sport in the Republic of Croatia (number 216-1080315-0302), Croatian Science Foundation (grant 8875) and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). SNP genotyping for CROATIA-Vis was performed by the Wellcome Trust Clinical Research Facility (WTCRF) at the Western General Hospital, Edinburgh, UK. CROATIA-Korcula was genotyped by Helmholtz Zentrum München, GmbH, Neuherberg, Germany and CROATIA-Split by AROS Applied Biotechnology, Aarhus, Denmark. We would like to acknowledge the invaluable contributions of the recruitment teams in Croatia (including those from the Institute of Anthropological Research in Zagreb and the Croatian Centre for Global Health at the University of Split), the administrative teams in Croatia and Edinburgh and the people of Korcula, Vis and Split.

## **EPIC**

**Investigators:** Jing Hua Zhao, Robert A Scott, Nicholas J Wareham.

**Contributions:** project conception, design and management: J.H.Z., R.A.S., N.J.W., phenotype collection and data management: J.H.Z., data analysis: J.H.Z., **Funding & Acknowledgements:** The EPIC Norfolk Study is funded by program grants from the Medical Research Council UK and Cancer Research UK, and by additional support from the European Union, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency, and the Wellcome Trust.

## **GS:SFHS**

**Investigators:** Lynne Hocking, Sandosh Padmanabhan, Generation Scotland, Holly Trochet.

**Contributions:** project conception, design and management: L.H., S.P., G.S., phenotype collection and data management: L.H., S.P., G.S., H.T. **Funding & Acknowledgements:** GS:SFHS is funded by the Scottish Executive Health Department, Chief Scientist Office, grant number CZD/16/6. Exome array genotyping for GS:SFHS was funded by the Medical Research Council UK and performed at the Wellcome Trust Clinical Research Facility Genetics Core at Western General Hospital, Edinburgh, UK. We would like to acknowledge the invaluable contributions of the families who took part in the

Generation Scotland: Scottish Family Health Study, the general practitioners and Scottish School of Primary Care for their help in recruiting them, and the whole Generation Scotland team, which includes academic researchers, IT staff, laboratory technicians, statisticians and research managers.

## H2000

**Investigators:** Markku Heliövaara, Mika Kähönen, Samuli Ripatti, Ida Surakka.

**Contributions:** project conception, design and management: M. Heliövaara, M.K., phenotype collection and data management: M. Heliövaara, M.K., S.R, I. Surakka, data analysis: M.K., S.R, I. Surakka

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## KORA F4

**Investigators:** Eva Albrecht, Harald Grallert, Joachim Heinrich, Janina S Ried.

**Contributions:** project conception, design and management: J. Heinrich, phenotype collection and data management: H.G., J.S.R., data analysis: E.A., J.S.R.

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## KORA S3

**Investigators:** Christian Gieger, Stefan Karrasch, Rajesh Rawal, Holger Schulz.

**Contributions:** project conception, design and management: C.G., S.K., H.S., phenotype collection and data management: C.G., S.K., R.R., H.S., data analysis: R.R.,

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## **LBC1936**

**Investigators:** Ian J Deary, Sarah E Harris, Lorna M Lopez, John M Starr

**Contributions:** project conception, design and management: I.J.D., J.M.S., phenotype collection and data management: I.J.D., S.E.H., L.M.L., J.M.S., data analysis: L.M.L. **Funding &**

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## **NFBC1966**

**Investigators:** Alexessander Couto Alves, Anna-Liisa Hartikainen, Momoko Horikoshi, Marjo-Riitta Jarvelin.

**Contributions:** project conception, design and management: M-R.J., phenotype collection and data management: A.C.A., A-L.H., M-R.J., data analysis: A.C.A., M. Horikoshi, M-R.J. **Funding &**

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## **NSPHS**

**Investigators:** Stefan Enroth, Ulf Gyllensten, Åsa Johansson.

**Contributions:** project conception, design and management: U.G., phenotype collection and data management: S.E., A.J., data analysis: S.E. **Funding & Acknowledgements:** U.G. acknowledges Swedish Medical Research Council (K2007-66X-20270-01-3, 2012-2884), Foundation for Strategic Research (SSF) and European Commission FP6 STRP (LSHG-CT-2006-01947). A.J. acknowledges Swedish Society for Medical Research (SSMF).

## ORCADES

**Investigators:** Harry Campbell, Peter K Joshi, Sarah H Wild, James F Wilson.

**Contributions:** project conception, design and management: H.C., S.H.W., J.F.W., phenotype collection and data management: H.C., S.H.W., J.F.W., data analysis: P.K.J. **Funding &**

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## SAPALDIA

**Investigators:** Medea Imboden, Ashish Kumar, Nicole M Probst-Hensch.

**Contributions:** project conception, design and management: N.M.P-H., phenotype collection and data management: M.I., A.K., N.M.P-H., data analysis: M.I., A.K., N.M.P-H. **Funding &**

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## SHIP

**Investigators:** Sven Gläser, Beate Koch, Alexander Teumer, Henry Völzke.

**Contributions:** project conception, design and management: S.G., B.K., H.V., phenotype collection and data management: S.G., B.K., A.T., H.V., data analysis: A.T. **Funding & Acknowledgements:**

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## YFS

**Investigators:** Nina Hutri-Kähönen, Terho Lehtimäki, Leo-Pekka Lyytikäinen, Olli T Raitakari.

**Contributions:** project conception, design and management: T.L., O.T.R., phenotype collection and data management: N.H-K., T.L., O.T.R., data analysis: L-P.L. **Funding & Acknowledgements:** The authors acknowledge Academy of Finland (126925, 121584, 124282), Academy of Finland (Eye) (134309), Academy of Finland (Salve) (129378), Academy of Finland (Gendi) (117787), Academy of Finland (Skidi) (41071), Social Insurance Institution of Finland, Tampere University Hospital Medical Funds (X51001 for T.L. ), Kuopio University Hospital Medical Funds, Turku University Hospital Medical Funds, Juho Vainio Foundation, Paavo Nurmi Foundation, Finnish Foundation of Cardiovascular Research (T.L.), Finnish Cultural Foundation, Tuberculosis Foundation (T.L.), Emil Aaltonen Foundation (T.L.), and Yrjö Jahnsson Foundation (T.L.).

## *Follow-up studies*

### ALSPAC

**Investigators:** David M Evans, Raquel Granell, John Henderson, John P Kemp.

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## ECRHS

**Investigators:** Claudia Flexeder, Juan R González, Joachim Heinrich, Deborah L Jarvis.

**Contributions:** project conception, design and management: J. Heinrich, D.L.J., phenotype collection and data management: J.R.G., J. Heinrich, D.L.J., data analysis: C.F. **Funding &**

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**Investigators:** Erik Ingelsson, Lars Lind, Anubha Mahajan, Andrew P Morris.

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## TwinsUK

**Investigators:** Chris J Hammond, Pirro G Hysi, Tim D Spector, Ana Viñuela.

**Contributions:** project conception, design and management: T.D.S., phenotype collection and data management: C.J.H., P.G.H., T.D.S., A.V., data analysis: P.G.H. **Funding & Acknowledgements:**

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## Lung eQTL study

**Investigators:** Yohan Bossé, Corry-Anke Brandsma, David C Nickle, Ma'en Obeidat, Don D Sin.

**Contributions:** phenotype collection and data management: Y.B., C-A.B., D.C.N., D.D.S., data analysis: M.O. **Funding & Acknowledgements:** The authors would like to thank the research staff at the Respiratory Health Network Tissue Bank of the FRQS for collecting lung specimens for the lung eQTL study at Laval University. Lung tissue eQTL study was funded by Merck Research Laboratories. M.O. is a Postdoctoral Fellow of the Michael Smith Foundation for Health Research (MSFHR) and the Canadian Institute for Health Research (CIHR) Integrated and Mentored Pulmonary and Cardiovascular Training program (IMPACT). Y.B. is the recipient of a Junior 2 Research Scholar award from the Fonds de recherche Québec – Santé (FRQS).

## **Supplementary Methods:**

### **Lung eQTL analyses**

Variants in 2Mb regions (new sentinel variant +/- 1Mb) which were in LD ( $r^2 > 0.3$ ) with the sentinel variant, for each of the 16 new sentinel variants, were assessed in a lung eQTL resource based on lung tissues of 1,111 individuals. Variants were selected if they (i) met an FDR threshold of 10%, and (ii) had eQTL  $P$  value  $< 5 \times 10^{-5}$ . In addition, for each probeset we ranked variants according to their correlation with the sentinel SNP (as measured by  $r^2$ ) first and to their eQTL  $P$  value second, and we only selected results for the top ranked variant for each probeset.

The descriptions of the lung eQTL dataset and subject demographics have been published previously<sup>7-9</sup>. Briefly, non-tumor lung tissues were collected from patients who underwent lung resection surgery at three participating sites: Laval University (Quebec City, Canada), University of Groningen (Groningen, The Netherlands), and University of British Columbia (Vancouver, Canada). Whole-genome gene expression and genotyping data were obtained from these specimens. Gene expression profiling was performed using an Affymetrix custom array (GPL10379) testing 51,627 non-control probe sets and normalized using RMA<sup>106</sup>. Genotyping was performed using the Illumina Human1M-Duo BeadChip array. Genotype imputation was undertaken using the 1000 Genomes Project<sup>107</sup> reference panel. Following standard microarray and genotyping quality controls, 1111 patients were available including 409 from Laval, 363 from Groningen, and 339 from UBC.

Association testing for each variant with mRNA expression in either *cis* (within 1 Mb of transcript start site) or in *trans* (all other eQTLs) was undertaken separately in each study, then their results were meta-analysed using inverse variance weighting meta-analysis and a 10% FDR genome-wide was applied. For the X chromosome only HapMap imputed data was available and the association testing was undertaken separately for males and females in each study.

## Blood eQTL analyses

Variants in 2Mb regions (new sentinel variant +/- 1Mb) which were in LD ( $r^2 > 0.3$ ) with the sentinel variant, for each of the 16 new sentinel variants, and were in HapMap were assessed in a publicly available blood eQTL dataset<sup>6</sup> with results from the analysis of 5,311 individuals. Association testing was undertaken both for *cis* (distance between the SNP and the probe midpoint < 250kb) and *trans* (distance between the SNP and the probe midpoint >5Mb) eQTL signals. No X chromosome data was available. Variants were selected if they (i) met an FDR threshold of 10%, and (ii) had eQTL *P* value <  $5 \times 10^{-5}$ . In addition, for each probeset we ranked variants according to their correlation with the sentinel SNP (as measured by  $r^2$ ) first and to their eQTL *P* value second, and we only selected results for the top ranked variant for each probeset.

## DNase hypersensitivity analysis

DNase hypersensitivity sites as defined by ENCODE<sup>108</sup> within 2Mb regions centred in the sentinel variant for the 16 new sentinel variants were accessed using the Uniform DNaseI HS track in the UCSC table browser<sup>109</sup> in the following cell types: A549, epithelial cell line derived from a lung carcinoma tissue; IMR90, fetal lung fibroblasts; AG04450, fetal lung fibroblast; BC\_Lung\_01-11002, lung, donor 01-11002, age 83, caucasian, DNA and RNA extract; BC\_Lung\_H12817N, lung, donor H12817N, age 71, caucasian, DNA and RNA extra; FibroP\_AG08396, lung fibroblasts taken from individuals with Parkinson's disease; HMVEC-LBI, blood microvascular endothelial cells, lung-derived; HMVEC-LLy, lymphatic microvascular endothelial cells, lung-derived; HPF, pulmonary fibroblasts isolated from lung tissue; HPAEC, pulmonary artery endothelial cells; HPAEpiC, pulmonary alveolar epithelial cells; HPAF, pulmonary artery fibroblasts; Lung\_BC, lung, parental cell type to donors 01-11002 and H12817N; Lung\_OC, primary frozen lung tissue from NICHD donor IDs 1104 (Rep B1

DNase), 602 (Rep B2 DNase), 1442 (Rep B3 DNase) and CF Center donor IDs DD006I (Rep B1 FAIRE) and DD007I (Rep B2 FAIRE); NHLF, lung fibroblasts; TBEC, trachea and bronchial epithelial cells from fresh lung tissue provided by National Disease Research Interchange, passage 2 primary, non-immortalized cells, donor was 21 years old; WI-38, embryonic lung fibroblast cells, hTERT immortalized, includes Raf1 construct. More details on cell type definitions can be found here <http://genome.ucsc.edu/ENCODE/cellTypes.html>. Sites for any cell which contained at least one variant strongly correlated ( $r^2 > 0.8$ ) with any of the new 16 sentinel variants were selected.

### **Conditional analysis: functional annotation**

In order to identify suggestive functional variants responsible for the new signals we observed or already known signals from previous GWAS studies<sup>13,15-17</sup>, 2Mb windows (1Mb either side of the sentinel SNP for the novel and known signals) were searched for functional variants. Variants were annotated using ENSEMBL's Variant Effect Predictor<sup>16</sup> and functional effects were predicted with SIFT<sup>17</sup>, PolyPhen-2<sup>18</sup>, CADD<sup>19</sup>, and GWAVA<sup>110</sup> databases. If a variant was annotated as 'deleterious' by SIFT, 'probably damaging' or 'potentially damaging' by PolyPhen-2, had a CADD scaled score  $\geq 20$  (CADD\_PHRED  $\geq 20$ ), or had a GWAVA score  $> 0.5$ , it was treated as a functional variant. CADD (Combined Annotation-Dependent Depletion) is a method for integrating many diverse annotations, namely conservation metrics, functional genomic data, transcript information, and protein level scores into a single score for each coding and noncoding variant. Scaled CADD score (CADD\_PHRED) ranks each variant relative to all possible substitutions of the human genome (~8.6 billion SNVs of the GRCh37/hg19 reference genome). A scaled CADD score greater or equal to 20 for a variant, indicates that the variant is within the 1% most deleterious variants in the human genome<sup>19</sup>. GWAVA (genome-wide annotation of variants) is a tool that combines information from a wide range of annotations to predict the functional impact of noncoding variants. We used a GWAVA score

threshold of 0.5, as proposed by authors, above which noncoding variants were considered as 'deleterious'<sup>110</sup>. Annotation results were filtered with VEP's --pick flag, which selects only one consequence per variant based on the canonical biotype status and length of the transcript as well as the ranking of the consequence type. For variants with multiple annotations, we selected the most deleterious annotation (i.e. if a variant was annotated as frameshift variant and intronic variant, the variant was considered to be frameshift). For each locus, functional variants that had a stage 1  $P$  value  $< 5 \times 10^{-4}$  or were in LD with the sentinel SNP ( $r^2 > 0.3$ ) were selected. Each functional variant was then tested jointly with the sentinel variant in the region, using GCTA<sup>20</sup> and data from 5,000 individuals from UK BiLEVE to estimate LD, to see whether the functional variant would explain for the signal. We considered that a signal was explained by a functional variant if the joint  $P$  value for the sentinel variant when fitted with the functional variant was  $> 0.01$ .

## Selection of priority genes

For each of the 16 loci that comprised the novel signals a small number of genes were selected as priority genes for subsequent analyses. These genes were selected according to the following criteria, based on eQTL results from blood and lung tissue for the sentinel variant in each region and for variants in LD ( $r^2 > 0.3$ ) with the sentinel (**Supplementary Table 3 a**), and the results of the conditional analysis on functional variants (**Supplementary Table 3 f**). eQTL results were restricted to variants that met a 10% FDR threshold and had eQTL  $P < 5 \times 10^{-5}$ . For each probeset, variants were ranked first according to  $r^2$  with the sentinel variant in the region, and second by the eQTL  $P$  value. Only the highest ranking variant was kept for each probeset. If the association of a sentinel variant was explained by a missense variant according to the conditional analysis, the gene where the missense variant lies was selected (this was the case for three regions: *GPR126*, *RIN3* and *LTBP4*). If no missense variant explained the association and no eQTL results met the FDR and  $P$  value

thresholds for a region, the gene closest to the sentinel variant was chosen (this was the case for three regions: *KCNS3*, *TBX3*, and *MN1*). If there was only evidence from blood eQTL up to two of the most significant genes that met the FDR and *P* value thresholds were selected (this was the case for one region: *NPNT*). In the *NPNT* region, *NPNT* was added to the list of priority genes as well as the genes implicated by the eQTL analysis, given the prior evidence of association with lung function for *NPNT*<sup>2</sup>. If there was evidence from lung tissue eQTL up to two of the most significant genes that met the FDR and *P* value thresholds for lung were selected (this was the case for 8 regions: *RNU5F-1*, *AK097794*, *ASTN2*, *LHX3*, *CCDC91*, *TRIP11*, *EMP2* and *AP1S2*), except for the *ENSA* region where an additional gene with a very significant *P* value for the blood eQTL ( $P > 5 \times 10^{-120}$ ) which also had a  $P < 5 \times 10^{-5}$  for lung tissue was included.

## **Messenger RNA sequencing**

Passage 3 normal human bronchial epithelial cells (NHBEs) (Lonza, UK), were cultured in growth factor-supplemented medium (BEGM, Lonza as described previously<sup>111</sup>). Cells were grown under these conditions and four different experimental conditions as part of a related RNA interference (RNAi) project each in three independent biological replicates (12 samples in total). Total RNA was extracted using established methods for RNA isolation (Sigma-Aldrich GenElute Mammalian Total RNA Miniprep Kit) and RNA quality was assessed for degradation on Agilent 2100 Bioanalyzer with all twelve samples having a RNA Integrity Number (RIN) at ~8 or above 8. The sequencing library was prepared with Illumina TruSeq RNA Sample Prep Kit v2. mRNA was poly-A selected by capturing total RNA samples with oligo-dT coated magnetic beads. The mRNA was then fragmented and randomly primed. cDNA was synthesised using random primers. Finally ready-for-sequencing library was prepared by end-repair, phosphorylation, A-tailing, adapter ligation and PCR amplification. Paired-end sequencing was performed on the Illumina HiSeq2000 platform using TruSeq v3

chemistry over 100 cycles yielding approximately 40 million reads per sample. The generated raw reads FastQ files (100 base pairs; Sanger / Illumina 1.9 encoding) were quality evaluated using FastQC. Mean quality scores across the bases for all reads in all twelve samples were above 28. Unmodified reads were used for subsequent analysis on Ubuntu 12.04 LTS operating system. Unspliced alignments onto human genome build GRCh37 were performed for each sample individually using Bowtie2 tool utilized by TopHat v2.0.12<sup>112</sup>. Reads aligning to more than 20 positions were discarded. The subset of reads that were not aligned uniquely were used by TopHat<sup>112</sup> to identify splice junctions. Cufflinks v2.2.1 programme<sup>113,114</sup> was used to assemble transcriptome for each individual sample. Transcriptomes from all the samples were merged using Cuffmerge v1.0.0 feature<sup>113,114</sup> in order to identify low-expression transcripts requiring deep sequencing coverage. The Cuffmerge<sup>113,114</sup> generated novel gene transfer format (GTF) annotation file was compared to Ensembl GTF annotation of GRCh37 genome build by using Cuffcompare v2.2.1<sup>113,114</sup>. All 12 NHBEc samples were used to identify reported and novel transcripts. The three untreated basal NHBEc samples were used to determine abundance under basal culture conditions, mean FPKM expressions of individual isoforms were calculated and their percentage of total transcripts expression determined. Splicing graphs depicting novel and known splice transcripts were generated using SpliceGrapher v0.2.4<sup>115</sup>.

## **Fetal differential expression**

Publically available Affymetrix U133 Plus 2 array data (Gene expression omnibus: GSE14334) of 38 fetal lung samples spanning the Pseudoglandular (7–16 weeks) and Canalicular (17–22 weeks) stages of lung development was mined as previously reported<sup>13</sup>. *P* values were adjusted for multiple testing using the Benjamini & Hochberg method<sup>14</sup>. Probes for each of a subset of genes in the 16 loci

(see criteria for selection in the “Selection of priority genes” section in the **Supplementary Methods**) were searched for within the results.

## **COPD differential expression**

Publically available microarray data (GSE37147<sup>15</sup>) was mined using GEO2R on the gene expression omnibus website (<http://www.ncbi.nlm.nih.gov/geo/info/geo2r.html>). Two sample groups were defined. Affymetrix Human ST1.0 array expression data, which includes one probe per gene, for 87 bronchial brushings in the lungs of individuals with COPD was defined as the first group, whilst the second group had the expression profiles of 151 bronchial brushings from ever smoker individuals without COPD. Differential expression between the 2 groups was identified using the default array statistics. *P* values were adjusted for multiple testing using the Benjamini & Hochberg method <sup>14</sup>. Probes for each of a subset of genes in the 16 loci (see criteria for selection in the “Selection of priority genes” section in the **Supplementary Methods**) were searched for within the results.

## **MAGENTA**

Stage 1 GWAS results were enriched for known biological pathways using MAGENTA v2<sup>116</sup>. MAGENTA defines a *P* value for each gene that is the lowest *P* value within 110kb upstream and 40kb downstream of the gene and is corrected for gene size, number of SNPs per gene and linkage disequilibrium within the region. For each gene set, the null hypothesis that there is a random distribution of gene association score ranks within the gene set is tested against the alternative hypothesis that there are more gene association score ranks above a given rank cut-off (75<sup>th</sup> percentile cut-off is recommended for polygenic traits) compared to random sampling of 10,000 gene sets of identical size. For each gene set, a false discovery rate (FDR) is calculated as the fraction of

all randomly sampled gene sets (10,000 x number of gene sets tested) that have more genes with  $P$  value below the cut off (75<sup>th</sup> percentile) than in the gene set being tested, divided by the fraction of real gene sets that have more genes with  $P$  value below the cut off (75<sup>th</sup> percentile) than in the gene set being tested.

Six databases of biological pathways were tested: including Ingenuity Pathway (June 2008, number of pathways  $n=81$ ), KEGG (2010,  $n=186$ ), PANTHER Molecular Function (January 2010,  $n=216$ ), PANTHER Biological Processes (January 2010,  $n=217$ ), PANTHER Pathways (January 2010,  $n=94$ ) and Gene Ontology (April 2010,  $n=1778$ ). Significance thresholds were Bonferroni corrected for each database.

Genes within 500kb either side from the sentinel variants were flagged in the analysis. Sensitivity analyses were run removing genes in the HLA region on chromosome 6.

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