ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original research article

A genome-wide association study of bronchodilator response in participants of European and African ancestry from six independent cohorts

Jessica D Gereige, Hanfei Xu, Victor E Ortega, Michael H Cho, Ming Liu, Phuwanat Sakornsakolpat, Edwin K Silverman, Terri H Beaty, Bruce E Miller, Per Bakke, Amund Gulsvik, Craig P Hersh, Jarrett D Morrow, International COPD Genetics Consortium, Elizabeth J Ampleford, Gregory A Hawkins, Eugene R Bleecker, Deborah A Meyers, Stephen P Peters, Juan C. Celedón, Kelan Tantisira, Jiang Li, Josée Dupuis, George T O'Connor

Please cite this article as: Gereige JD, Xu H, Ortega VE, *et al*. A genome-wide association study of bronchodilator response in participants of European and African ancestry from six independent cohorts. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00484-2021).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Title: A genome-wide association study of bronchodilator response in participants of European and African ancestry from six independent cohorts

Jessica D Gereige[1,2], Hanfei Xu[3], Victor E Ortega[4], Michael H Cho[5], Ming Liu[5,12], Phuwanat Sakornsakolpat[5], Edwin K Silverman[5], Terri H Beaty[6], Bruce E Miller[7], Per Bakke[8], Amund Gulsvik[8], Craig P Hersh[5], Jarrett D Morrow[5], International COPD Genetics Consortium, Elizabeth J Ampleford[4], Gregory A Hawkins[4], Eugene R Bleecker[4], Deborah A Meyers[4], Stephen P Peters[4], Juan C. Celedón[9], Kelan Tantisira[10], Jiang Li[5,11], Josée Dupuis[3], George T O'Connor[1,2]

1. Division of Pulmonary, Allergy, Sleep, and Critical Care Medicine, Boston Medical Center, Boston, Massachusetts.
2. Pulmonary Center, Boston University School of Medicine, Boston, Massachusetts.
3. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts.
4. Center for Precision Medicine, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina.
5. Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.
6. Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA.
7. GSK R&D, Collegeville, Pennsylvania, USA.
8. Department of Clinical Science, University of Bergen, Bergen, Norway.
9. Division of Pediatric Pulmonary Medicine, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, PA.
10. Division of Pediatric Respiratory Medicine, University of California and Rady Children's Hospital, San Diego, California
11. Research Center, The Seventh Affiliated Hospital of Sun Yat-Sen University, Shenzhen, Guangdong, China
12. Bioinformatics and Computational Biology Program, Worcester Polytechnic Institute, Worcester, MA

Corresponding author: Jessica Gereige, MD, Pulmonary Center, Boston University School of Medicine, 72 E. Concord St, R3, Boston, MA 02118. Email: jessikag@bu.edu

Key Message

While no genetic variant reached genome-wide significance in a multi-ethnic GWAS of bronchodilator response, genes of interest include *FREM1*, *ZNF284*, and *ATP2C2.*

Abstract

Introduction: Bronchodilator response (BDR) is a measurement of acute bronchodilation in response to short-acting β2-agonists (SABA), with a heritability between 10-40%. Identifying genetic variants associated with BDR may lead to a better understanding of its complex pathophysiology.

Methods: We performed a genome-wide association study (GWAS) of BDR in six adult cohorts with participants of European ancestry (EA) and African ancestry (AA) including community cohorts and cohorts ascertained on the basis of obstructive pulmonary disease. Validation analysis was carried out in two pediatric asthma cohorts.

Results: A total of 10,623 EA and 3,597 AA participants were included in the analyses. No single nucleotide polymorphism (SNP) was associated with BDR at the conventional genome-wide significance threshold ($p<5x10^{-8}$). Performing fine-mapping and using a threshold of $p<5\times10^{-6}$ to identify suggestive variants of interest, we identified three SNPs with possible biological relevance: rs35870000 (within *FREM1*), which may be involved in IgE- and IL5-induced changes in airway smooth muscle cell responsiveness; rs10426116 (within *ZNF284*), a zinc finger protein, which have been implicated in asthma and BDR previously; rs4782614 (near *ATP2C2)*, involved in calcium transmembrane transport. Validation in pediatric cohorts yielded no significant SNPs, possibly due to age-genotype interaction effects.

Conclusion: Ancestry-stratified and ancestry-combined GWAS meta-analyses of over 14,000 participants did not identify genetic variants associated with BDR at the genome-wide significance threshold, although a less stringent threshold identified three variants showing suggestive evidence of association. A common definition and protocol for measuring BDR in research may improve future efforts to identify variants associated with BDR.

Manuscript

Introduction

Chronic lower respiratory diseases, which include asthma and chronic obstructive pulmonary disease (COPD), impose a major global health burden, affecting more than 530 million people [1]. The first-line treatment for asthma and COPD patients includes targeting airway hyperresponsiveness by use of β2-agonists which act on β2-adrenergic receptors located on airway smooth muscle (ASM) cells in the lower respiratory tract, resulting in muscle relaxation and bronchodilation [2]. While measurement of airway hyperresponsiveness is occasionally used as a diagnostic tool for asthma, measuring acute bronchodilation in response to short-acting β2-agonists (SABA) is more widely used to differentiate fixed from reversible airflow obstruction and determine response to treatment.

Acute bronchodilation in response to pharmacologic bronchodilator, referred to as bronchodilator response (BDR), is often defined as the percent change in forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) occurring approximately 15 minutes after inhalation of a SABA. In the general population, most individuals have little response to medication with 95% of asymptomatic never smoker adults experiencing an increase in FEV1 of 9% or less after SABA use [3]. However, this response is variable and can be influenced by factors such as presence of symptoms [4], and smoking and anthropometric measurements which are thought to explain 7-16% of the variability in BDR [5]. At least a portion of this variability appears to be influenced by genetics and has been cited to range between 10-40% [6], [7]. Determining the genetic variants associated with BDR may lead to a better understanding of the pathophysiology underlying this important measure of airway disease and response to treatment.

Candidate genes reported to be associated with BDR include the β2-adrenergic receptor (*ADRB2*)[8], adenylyl cyclase type 9 (*ADCY9*) [9], corticotrophin-releasing hormone receptor 2 (*CRHR2*) [10], and arginase 1 (*ARG1*) [11]. Genome-wide association studies (GWASs) and a whole-genome sequencing pharmacogenetic study of BDR in asthma and COPD participants have identified genetic variants from a number of genes, highlighting the different biological pathways likely involved in controlling BDR [12]–[19]. These studies suggest that BDR is a complex trait related to multiple mechanisms involving more than the β2-adrenergic receptors alone.

However, the reported associations identified thus far by GWASs have shown limited replication across studies. While this lack of replication may be related to differences in study population characteristics (such as age, race/ethnicity, lung pathology) or gene-environment interactions [6], [20], the range of reported associations indicate the complexity of this trait and the need for further studies to replicate these previous findings or identify new genetic variants associated with BDR mechanistic pathways.

By including a large number of cohorts with participants of both African and European ancestry, and participants from asthma and COPD cohorts as well as participants from a community-based study which did not recruit participants based on disease or smoking status, the aim of these ancestry-stratified and ancestry-combined GWAS meta-analyses of BDR was to identify and replicate genetic variants associated with BDR . We sought to further support our findings

through validation analyses that were undertaken in two pediatric asthma cohorts of European ancestry and Hispanic/Latino ethnicity.

Methods

Study Population

Six non-overlapping cohorts contributed to our primary analysis: the Framingham Heart Study (FHS) [21]; Genetic Epidemiology of COPD (COPDGene) [22]; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) [23]; Treatment of Emphysema with a Gamma-Selective Retinoid Agonist (TESRA) [24]; the Bergen, Norway COPD Cohort, Genetics of Chronic Obstructive Lung Disease (GenKOLS) [25]; and the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) [26]. To assess whether associations observed among adults are also present among children, we used two pediatric asthma cohorts – the Genetics of Asthma in Costa Rica Study (GACRS) [27] and the Childhood Asthma Management Program (CAMP) [28]. All cohorts have participants who self-identify as being of European ancestry (EA), and two cohorts (COPDGene and SPIROMICS) also have participants who self-identify as being of African ancestry (AA). All study protocols were approved by the respective local Institutional Review Boards, and written informed consent for genetic studies was obtained from all participants or their parents, in the case of pediatric participants.

Spirometry and bronchodilator response

Standardized spirometry was performed in all study cohorts according to the 2005 European Respiratory Society - American Thoracic Society guidelines [29]. BDR was measured as a

percent change in FEV1 and FVC following the administration of 180μg (2 inhalations) of albuterol for participants in FHS and COPDGene and 400μg of salbutamol for participants in ECLIPSE and GenKOLS. For participants in SPIROMICS, BDR was measured following the administration of 360μg (4 inhalations) of albuterol and 68μg (4 inhalations) of ipratropium bromide.

Genotyping and quality control

Different genotyping platforms were used across these cohorts, details of which can be found in Table S1. Genotyped SNPs were excluded if they had a high missingness rate (cohort-specific thresholds ranged between 1-5%), significant departure from Hardy Weinberg equilibrium, high discordance rates between duplicated samples, and if they were monomorphic in the sample or had low minor allele frequency (MAF<1%). Imputation was performed using the Haplotype Reference Consortium (HRC) [30] reference panel or 1000 Genomes Project [31]. For each cohort, SNPs with poor imputation quality (imputation quality r-squared ≤ 0.3) were excluded from further analysis. Quantile-quantile (Q-Q) plots are provided in Figure S1.

Statistical Analysis

Two BDR phenotypes (Percent change of FEV1 and Percent change of FVC) were defined as our primary outcomes:

$$\text{Percent change of FEV1} = 100 \times (\text{Post\_FEV1} - \text{Pre\_FEV1})/\text{Pre\_FEV1}$$

$$\text{Percent change of FVC} = 100 \times (\text{Post\_FVC} - \text{Pre\_FVC})/\text{Pre\_FVC}$$

The analyses were adjusted for age at baseline (year), sex, smoking status, average of the pre-bronchodilator and post-bronchodilator value of FEV1 or FVC, and cohort-specific significant principal components of ancestry to account for population stratification. We included participants who have both pre- and post- bronchodilator measures for FEV1 and FVC available and had no missing covariates, excluding outliers defined as participants with an FEV1 or FVC bronchodilator response falling outside of 3 standard deviations from the mean value for each phenotype. We also excluded participants with percent change of FEV1 >100% or percent change of FVC >100%.

Association analyses of SNPs were performed in each cohort using multiple linear regression models adjusting for covariates, for each outcome. The primary meta-analysis was stratified by ancestry group to minimize the effects of heterogeneity; this analysis is referred to as the stratified meta-analysis. A secondary analysis was performed by combining the EA and AA participants; the results of this secondary analysis are reported separately and referred to as the combined meta-analysis. We used a linear mixed effects model to account for familial relatedness in the FHS cohort, using expected kinship coefficient within family. Ancestry-specific inverse-variance-weighted fixed-effects meta-analysis was performed using METAL software [32]. We considered SNPs with p-value $< 5\times10^{-8}$ as genome-wide significant [33]. We performed validation analyses on two separate pediatric asthma cohorts, of different genetic ancestry, using the same analysis strategy.

We then performed a linkage disequilibrium (LD) clumping procedure to identify distinct signals using the software PLINK. The top associated SNPs (p-value$<5\times10^{-6}$) located in close physical

proximity (±1Mb) were clumped by LD measured by r^2 >0.05, and only the strongest trait-associated SNP within each LD block was kept, using CEU and YRI individuals from the 1000 Genomes (phase 1 version 3) as reference panels for EA and AA groups, respectively [34].

Validation in pediatric cohort

Validation analysis was carried out on EA participants in the CAMP study and Hispanic/Latino participants in the GACRS study using the SNPs identified from the discovery analysis (SNPs with association $p < 5x10^{-6}$ and MAF>=5%). Bonferroni-adjusted p-value thresholds were used: p<0.05/131=0.0004 for the stratified meta-analysis, and p<0.05/57=0.0009 for the combined meta-analysis.

Replication of previously reported BDR genetic variants

We then searched the literature for SNPs that have reached genome-wide significance ($p<5\times10^{-8}$) in GWASs of BDR. Other BDR GWASs include SHARP (which combined data from CAMP, CARE, and ACRN), SAGE I, SAGE II, GALA II, and COPDGene. Participants in these published studies included children and adults of African, European, and Hispanic/Latino ancestry with asthma or COPD. Because one of the cohorts in our meta-analysis was the COPDGene cohort, we repeated our analysis excluding all participants from this cohort for comparison. We also evaluated SNPs previously reported to be associated with asthma from a large multiancestry GWAS meta-analysis, as well as SNPs associated with COPD from several GWASs (Table S4; includes references). A Bonferroni-adjusted p-value threshold of 0.0003 (0.05/143) was used to account for the total number of SNPs from the literature that were evaluated (n=143).

Fine Mapping using PAINTOR

We used ancestry-specific LD reference panels to conduct fine-mapping analyses to help identify likely causal variants within 250 kb flanking each of the strongest trait-associated SNP identified above, using PAINTOR (Probabilistic Annotation INTegratOR) software [35]. PAINTOR is a software which integrates the strength of association signals from a test of association considering both LD structure and functional annotation information to calculate a posterior probability for each SNP as the source of the association signal in a region. We used PAINTOR utilities to obtain the LD correlation matrix for each locus using the 1000 Genomes phase 3 as the reference panels for EA and AA analyses separately [31]. We considered the following functional annotation categories from the annotation library provided by PAINTOR [36]: (1) lung related annotations (E096); (2) fetal lung related annotations (E88); (3) fetal lung fibroblast cell line related annotations (E017); (4) lung fibroblast primary cell related annotations (E128); (5) smooth muscle related annotations (E076, E078, E111). We first ran PAINTOR on each functional annotation separately and prioritized annotations based on the improvement in the fit of the model. Since none of the SNPs were labeled with any of the specified functional annotations, we ran a final PAINTOR model without any annotations to calculate the posterior probability for each SNP within our fine-mapping loci.

Results

Descriptive Characteristics of Study Cohorts

The baseline characteristics of all cohorts and participants included in the analyses are shown in Table 1. A total of 10,623 participants of EA and 3,597 participants of AA were included in the

association analyses. TESRA differed from the remainder of the cohorts in that there were no individuals diagnosed with asthma in this cohort, and all reported smokers had a prior history of smoking but were not active smokers at the time of enrollment into the study. GENKOLS and FHS participants had the lowest reported average number of pack-years of smoking; by design the FHS participants included never-smokers while GENKOLS only enrolled current or former smokers. Description of pediatric cohorts can be found in the online supplement.

GWAS results from meta-analysis of adult cohorts

In the primary, ancestry-stratified meta-analysis of adult participants in the FHS, COPDGene, ECLIPSE, GENKOLS, TESRA, and SPIROMICS samples, no BDR-SNP association achieved genome-wide significance ($p < 5\times10^{-8}$). We only report results of variants with a minor allele frequency (MAF) of 5% or greater. A total of 131 SNPs were associated with BDR at $p<5\times10^{-6}$, commonly considered as 'suggestive' evidence of association (Table S2). SNPs with an association $p < 5\times10^{-6}$ after LD clumping are shown in Table 2. In the secondary, combined meta-analysis, a total of 57 SNPs were associated with BDR at $p<5\times10^{-6}$ (Table S2), 21 SNPs after LD clumping (Table 2), and one SNP (rs4782614) associated with BDR as defined by percent change in FEV1 nearing significance ($p=7.5\times10^{-8}$). Manhattan plots for these analyses are shown in Figure 1 (stratified meta-analysis) and Figure 2 (combined meta-analysis), and the Q-Q plots in Figures S1 and S2. Table S5 contains cohort-specific results.

Validation in pediatric cohort

Validation analyses yielded no significant associations after adjusting for multiple comparisons ($p < 0.05/342=0.00015$ for the stratified meta-analysis, and $p<0.05/57=0.0009$ for the combined meta-analysis) (Table S3). A test of proportions to compare the direction of effect of those SNPs

identified in the validation analysis yielded p=0.005 for CAMP and p=0.57 for GACRS. Therefore, the direction of effect in the CAMP study, in which participants are EA, was consistent with the direction in our primary analysis, while that in GACRS, which is made up of Hispanic/Latino participants, was not.

Replication of BDR, COPD, and asthma previously reported SNPs

None of the SNPs that have previously attained genome-wide statistical significance in published GWASs of BDR [12]–[19], COPD, or asthma reached statistical significance in our analysis after correcting for multiple-comparisons ($p<0.0003$) (Table S4).

Fine Mapping and Regional Plots for biologically relevant SNPs

We performed fine mapping and examined regional plots for the SNPs showing 'suggestive' evidence of an association (i.e. $p<5\times10^{-6}$) in the ancestry-stratified meta-analysis to identify the most relevant signals. We examined SNPs with a posterior probability above 70% after fine mapping to narrow our focus on variants of potential interest (Table 3). A total of 7 SNPs with MAF>=5% and a BDR-association $p<5\times10^{-6}$ had a posterior probability greater than 70%. For these 7 SNPs, the number of SNPs included in the 95% credible sets ranged from 2 to 8. We examined the genes that are most closely associated with these SNPs for possible biological relevance in BDR. Regional plots for the two genes encoding proteins in biological pathways plausibly related to BDR based on fine mapping results among participants of AA (*FREM1* and *ZNF284*) are shown in Figure 3. There were no significant recombination peaks between *FREM1* and rs35870000 or between *ZNF284* and rs10426116, indicating the signal for association obtained from these two SNPs in our study may be related to these two genes. The regional plot

for the SNP showing the strongest association in the combined meta-analysis, rs4782614 ($p=7.5x10^{-8}$), is shown in Figure 4.

Expression Quantitative Trait Loci in Lung and Whole Blood

Next, we examined whether 'suggestive' SNPs from our study with $p<5\times10^{-6}$ had previously been reported as significant expression quantitative trait loci (eQTLs) in lung tissue and whole blood using data from the Genotype Tissue Expression (GTEx) Project. A total of 10 SNPs from the stratified meta-analysis and four SNPs from the combined meta-analysis matched previously reported eQTLs from GTEx samples of lung and whole blood (Table 4). The rs35870000 SNP is an eQTL for RP11-408A13.4 in whole blood, although there is no known clinical significance for this gene. The rs4782614 SNP is located near the *ATP2C2* gene and is an eQTL for *ATP2C2* in whole blood.

Discussion

In this GWAS meta-analysis of BDR no SNP reached genome-wide significance in association with either percent change in FEV1 or percent change in FVC. This study has a number of strengths that represent an important contribution to the literature on the genetics of BDR which include using a large number of independent cohorts, having participants of both African and European ancestry in the primary analysis, and of Hispanic/Latino ancestry in the validation analysis, and finally, the inclusion of participants with and without obstructive lung disease. With a total of 10,623 participants of EA and 3,597 participants of AA, this study had 80% power to detect SNPs explaining 0.4% and 1.1% of the variance in the outcome for our stratified EA and AA analyses, respectively, at a genome-wide significance level of 5×10^{-8}. Therefore, we had adequate power to detect SNPs with small effects among EA participants and SNPs with

larger effects among AA participants. However, despite having adequate power, we were unable to replicate findings of previous GWASs, even at a higher p-value cutoff ($p<5x10^{-6}$). Although this is a negative finding, it is nonetheless an important one given the size of this meta-GWAS.

Unlike GWASs for disease phenotypes, such as asthma, or spirometric measurements of pulmonary function, such as the FEV1/FVC ratio, genetic variants reported to be associated with BDR have not been well replicated across studies. This lack of replication is likely due to a number of factors including the physiologic complexity of the BDR phenotype, variation in the definition of BDR across studies, as well as variations in medication protocols used in different studies, between-study differences in race/ethnicity and pulmonary pathology, and finally, environmental factors affecting BDR. For example, there is evidence that at least one environmental factor, inhaled corticosteroid treatment, can modulate the effect of a gene on BDR response [20]. Environmental factors that increase airway inflammation or epithelial injury may also modify the effects of genetic variants on observed BDR, but further gene-environment interaction studies of BDR are needed to identify such interactions. Unfortunately, gene-environment interaction studies require a very large number of participants before adequate statistical power is achieved.

The findings of our study and previous GWAS studies of BDR reinforce the notion that the molecular pathways influencing BDR are complex and involve multiple genes. While no SNP reached genome-wide significance in our analyses, several genes that lie in close proximity to SNPs with p-values that suggested association ($p<5x10^{-6}$) and may have biological functions that could influence BDR. Using fine-mapping and regional plots to hone in on signals of potential

biological importance, we highlight three SNPs that, to our knowledge, have not been previously reported as being associated with BDR: rs35870000 and rs10426116, both of which had suggestive associations with BDR as defined by percent change in FEV1 ($p=3.4x10^{-6}$ and $p=1.1x10^{-6}$ respectively) only among participants of AA in the stratified meta-analysis, and rs4782614 which had a suggestive association with BDR as defined by percent change in FEV1 ($p= 7.53x10^{-8}$) and FVC ($p=2.53x10^{-6}$) in the combined meta-analysis.

The rs35870000 SNP is a missense variant located within the gene *FREM1* (FRAS1 related ECM1), with no other known genes within 60kbp of this SNP. The Toll-like/IL-1 receptor regulator (TILRR) which regulates the IL-1 receptor type I (IL1R1) is encoded by a spliced variant of this *FREM1*gene [37]. Inhibition of IL1R1 has been shown to decrease IL-5- and IgE-induced changes in ASM responsiveness [38]. It is therefore conceivable that ASM contraction, and by extension BDR, can be modulated by *FREM1* through the action of cytokines widely implicated in asthma pathophysiology. Notably, the association between rs35870000 with BDR was seen in the AA sub-group in our study, a population in which anti-IL-5 therapy has been reported to be most effective [39].

The rs10426116 SNP lies within the *ZNF284* (zinc finger protein 284) gene on chromosome 19 and is a 3' UTR variant (the 3'UTR region often contains regulatory regions that influence gene expression). In a gene-environment study of BDR, a region on chromosome 19 containing multiple zinc finger proteins was identified as showing an association with BDR that was modified by inhaled corticosteroids [20]. As pointed out by the authors of that study, and corroborated by the findings of the current study, further exploration of the mechanisms by which zinc finger proteins affect BDR may be worth pursuing.

The rs4782614 SNP lies within 6023bp from the *ATP2C2* (ATPase secretory pathway Ca^{2+} transportin 2) gene, and is a significant eQTL for *ATP2C2* in whole blood (as reported in GTEx). The *ATP2C2* gene encodes the calcium-ATPase SPCA2 protein that is highly expressed in the Golgi apparatus and plays an important role in calcium homeostasis [40], an essential component of muscle contraction. Furthermore, intronic SNPs near *ATP2C2* have been associated with frequent COPD exacerbations in a COPD GWAS [41]. Notably, and perhaps not surprisingly, other GWASs have reported enrichement of ion channels in association with BDR [16].

A major limitation of our findings is the lack of genome-wide significant associations despite our large sample size attained by pooling several studies. Although SNPs with nominally significant ($p<5x10^{-6}$) associations with BDR are highlighted above, none reached conventional genome-wide significance, despite combined samples sizes of 10,623 EA and 3,597 AA participants. In addition, our validation cohorts were fundamentally different than the discovery cohorts in that they were pediatric studies of asthma and did not include participants with AA. Associations observed in adults might not be present in children, especially given the possible presence of age-by-genotype interaction that has been previously reported [42]. Heterogeneity across studies included in the meta-analysis and in the pediatric cohorts may have limited our ability to detect genome-wide associations. One potential source of such heterogeneity is the difference in the medication protocols that were used to obtain the BDR in the various studies. The ascertainment of race and ethnicity by self-report leads to uncertainty regarding admixture of genetic ancestries and may be confounded by aspects of social identity, but it is unlikely to be a limitation in this study as we controlled for ancestry by including principal components as covariates in our model. Finally, another limitation relevant to all GWASs, including this one, is that the studied

SNPs are often in linkage disequilibrium with the causal variants, and further experimental validation will be required to move from statistical association to mechanistic inferences about causation.

Future studies should consider including gene-environment interactions when studying BDR, such as the effect of first-hand and second-hand smoking or the use of inhaled corticosteroids, as this may help tease out the most important association signals related to BDR. Consideration of alternative, and unified, methods of defining BDR for research purposes should also be evaluated.

Acknowledgements

The Genotype-Tissue Expression (GTEx) Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. The data used for the analyses described in this manuscript were obtained from the GTEx Portal on August 7, 2020.

We would like to acknowledge Achilleas Pitsillides, PhD for the help and support he provided in the use of GTEx. The authors also acknowledge the patients, families, recruiters, health care providers, and community clinics for their participation in FHS, COPDGene, ECLIPSE, TESRA, GenKOLS, SPIROMICS, GACRS, and CAMP.

Financial Statement: This work was supported by the National Institutes of Health through a Ruth L. Kirschstein National Research Service Award 5T32HL007035 (JDG), R01 HL142992 (VEO), NIH U01 HL65899 and NIH R01 HL127332 (KT), NIH R01HL130512 (CH), R01HL149861, R01HL137927, R01 HL089856, and R01HL147148 (MHC). The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University (Contract No. N01-HC-25195, HHSN268201500001I and 75N92019D00031). SPIROMICS was supported by U01 HL137880 and contracts from the NHLBI (HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, HHSN268200900020C) which were supplemented by contributions made through the Foundation for the NIH from AstraZeneca; Bellerophon Therapeutics; Boehringer-Ingelheim Pharmaceuticals, Inc; Chiesi Farmaceutici SpA; Forest Research Institute, Inc; GSK; Grifols Therapeutics, Inc; Ikaria, Inc; Nycomed GmbH; Takeda Pharmaceutical Company; Novartis Pharmaceuticals Corporation; Regeneron Pharmaceuticals, Inc; and Sanofi. COPDGene was supported by Award Number U01 HL089897 and Award Number U01 HL089856 from the National Heart, Lung, and Blood Institute. COPDGene is also supported by the COPD Foundation through contributions made to an Industry Advisory Board that has included AstraZeneca, Bayer Pharmaceuticals, Boehringer- Ingelheim, Genentech, GlaxoSmithKline, Novartis, Pfizer, and Sunovion. ECLIPSE and GenKOLS were supported by GlaxoSmithKline. TESRA was supported by Roche. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

References

[1] J. B. Soriano *et al.*, "Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015," *Lancet Respir. Med.*, vol. 5, no. 9, pp. 691–706, Sep. 2017.

[2] J. L. Benovic, "Novel β2-adrenergic receptor signaling pathways," in *Journal of Allergy and Clinical Immunology*, 2002, vol. 110, no. 6 SUPPL.

[3] R. E. Dales, W. O. Spitzer, P. Tousignant, M. Schechter, and S. Suissa, "Clinical interpretation of airway response to a bronchodilator. Epidemiologic considerations," *Am. Rev. Respir. Dis.*, vol. 138, no. 2, pp. 317–320, 1988.

[4] S. Lehmann, P. S. Bakke, G. E. Eide, and A. Gulsvik, "Bronchodilator response to adrenergic β2-agonists: Relationship to symptoms in an adult community," *Respir. Med.*, vol. 101, no. 6, pp. 1183–1190, Jun. 2007.

[5] S. Lehmann, P. S. Bakke, G. E. Eide, S. Humerfelt, and A. Gulsvik, "Bronchodilator reversibility testing in an adult general population; The importance of smoking and anthropometrical variables on the response to a β2-agonist," *Pulm. Pharmacol. Ther.*, vol. 19, no. 4, pp. 272–280, Aug. 2006.

[6] V. E. Ortega and D. A. Meyers, "Pharmacogenetics: implications of race and ethnicity on defining genetic profiles for personalized medicine.," *J. Allergy Clin. Immunol.*, vol. 133, no. 1, pp. 16–26, Jan. 2014.

[7] M. J. Mcgeachie *et al.*, "Polygenic heritability estimates in pharmacogenetics: Focus on asthma and related phenotypes," *Pharmacogenet. Genomics*, vol. 23, no. 6, pp. 324–328, 2013.

[8] N. Hizawa, "Beta-2 adrenergic receptor genetic polymorphisms and asthma," *Journal of Clinical Pharmacy and Therapeutics*, vol. 34, no. 6. pp. 631–643, Dec-2009.

[9] S. H. Kim, Y. M. Ye, H. Y. Lee, H. J. Sin, and H. S. Park, "Combined pharmacogenetic effect of ADCY9 and ADRB2 gene polymorphisms on the bronchodilator response to inhaled combination therapy," *J. Clin. Pharm. Ther.*, vol. 36, no. 3, pp. 399–405, Jun. 2011.

[10] A. H. Poon *et al.*, "Association of corticotropin-releasing hormone receptor-2 genetic variants with acute bronchodilator response in asthma," *Pharmacogenet. Genomics*, vol. 18, no. 5, pp. 373–382, May 2008.

[11] A. A. Litonjua *et al.*, "ARG1 is a novel bronchodilator response gene: Screening and replication in four asthma cohorts," *Am. J. Respir. Crit. Care Med.*, vol. 178, no. 7, pp. 688–694, Oct. 2008.

[12] E. Israel *et al.*, "Genome-wide association study of short-acting β2-agonists. A novel genome-wide significant locus on chromosome 2 near ASB3.," *Am. J. Respir. Crit. Care Med.*, vol. 191, no. 5, pp. 530–7, Mar. 2015.

[13] K. A. Drake *et al.*, "A genome-wide association study of bronchodilator response in Latinos implicates rare variants.," *J. Allergy Clin. Immunol.*, vol. 133, no. 2, pp. 370–8, Feb. 2014.

[14] Q. L. Duan *et al.*, "A genome-wide association study of bronchodilator response in asthmatics.," *Pharmacogenomics J.*, vol. 14, no. 1, pp. 41–7, Feb. 2014.

[15] B. E. Himes *et al.*, "Genome-wide association analysis in asthma subjects identifies SPATS2L as a novel bronchodilator response gene.," *PLoS Genet.*, vol. 8, no. 7, p.

e1002824, Jul. 2012.
[16] M. Hardin *et al.*, "A genome-wide analysis of the response to inhaled β2-agonists in chronic obstructive pulmonary disease.," *Pharmacogenomics J.*, vol. 16, no. 4, pp. 326–35, 2016.
[17] B. Padhukasahasram *et al.*, "Gene-based association identifies SPATA13-AS1 as a pharmacogenomic predictor of inhaled short-acting beta-agonist response in multiple population groups," *Pharmacogenomics J.*, vol. 14, no. 4, pp. 365–371, 2014.
[18] M. L. Spear *et al.*, "A genome-wide association and admixture mapping study of bronchodilator drug response in African Americans with asthma.," *Pharmacogenomics J.*, vol. 19, no. 3, pp. 249–259, 2019.
[19] A. C. Y. Mak *et al.*, "Whole-Genome Sequencing of Pharmacogenetic Drug Response in Racially Diverse Children with Asthma.," *Am. J. Respir. Crit. Care Med.*, vol. 197, no. 12, pp. 1552–1564, 2018.
[20] A. C. Wu *et al.*, "Inhaled corticosteroid treatment modulates ZNF432 gene variant's effect on bronchodilator response in asthmatics," *J. Allergy Clin. Immunol.*, vol. 133, no. 3, pp. 723-728.e3, Mar. 2014.
[21] G. L. Splansky *et al.*, "The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination.," *Am. J. Epidemiol.*, vol. 165, no. 11, pp. 1328–35, Jun. 2007.
[22] E. A. Regan *et al.*, "Genetic epidemiology of COPD (COPDGene) study design," *COPD J. Chronic Obstr. Pulm. Dis.*, vol. 7, no. 1, pp. 32–43, Feb. 2010.
[23] J. Vestbo *et al.*, "Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE)," *Eur. Respir. J.*, vol. 31, no. 4, pp. 869–873, Apr. 2008.
[24] P. W. Jones and A. D. Rames, "TESRA (Treatment Of Emphysema With A Selective Retinoid Agonist) Study Results," in *American Thoracic Society International Conference Meetings Abstracts American Thoracic Society International Conference Meetings Abstracts*, 2011, pp. A6418–A6418.
[25] T. B. Grydeland *et al.*, "Quantitative computed tomography: Emphysema and airway wall thickness by sex, age and smoking," *Eur. Respir. J.*, vol. 34, no. 4, pp. 858–865, Oct. 2009.
[26] D. Couper *et al.*, "Design of the subpopulations and intermediate outcomes in copd study (SPIROMICS)," *Thorax*, vol. 69, no. 5, pp. 491–494, 2014.
[27] G. M. Hunninghake *et al.*, "Sensitization to Ascaris lumbricoides and severity of childhood asthma in Costa Rica," *J. Allergy Clin. Immunol.*, vol. 119, no. 3, pp. 654–661, Mar. 2007.
[28] "The Childhood Asthma Management Program (CAMP): design, rationale, and methods. Childhood Asthma Management Program Research Group - PubMed," *Control Clin Trials*, vol. 20, no. 1, pp. 91–120.
[29] M. R. Miller *et al.*, "Standardisation of spirometry," *European Respiratory Journal*, vol. 26, no. 2. Eur Respir J, pp. 319–338, Aug-2005.
[30] S. McCarthy *et al.*, "A reference panel of 64,976 haplotypes for genotype imputation," *Nat. Genet.*, vol. 48, no. 10, pp. 1279–1283, Oct. 2016.
[31] A. Auton *et al.*, "A global reference for human genetic variation," *Nature*, vol. 526, no. 7571. Nature Publishing Group, pp. 68–74, 30-Sep-2015.
[32] C. J. Willer, Y. Li, and G. R. Abecasis, "METAL: fast and efficient meta-analysis of genomewide association scans.," *Bioinformatics*, vol. 26, no. 17, pp. 2190–1, Sep. 2010.

[33] I. Pe'er, R. Yelensky, D. Altshuler, and M. J. Daly, "Estimation of the multiple testing burden for genomewide association studies of nearly all common variants," *Genet. Epidemiol.*, vol. 32, no. 4, pp. 381–385, May 2008.
[34] D. M. Altshuler *et al.*, "An integrated map of genetic variation from 1,092 human genomes," *Nature*, vol. 491, no. 7422, pp. 56–65, Nov. 2012.
[35] G. Kichaev *et al.*, "Integrating Functional Data to Prioritize Causal Variants in Statistical Fine-Mapping Studies," *PLoS Genet.*, vol. 10, no. 10, Oct. 2014.
[36] "2b. Overlapping annotations." [Online]. Available: https://github.com/gkichaev/PAINTOR_V3.0/wiki/2b.-Overlapping-annotations. [Accessed: 12-Jan-2021].
[37] M. A. Kashem *et al.*, "Toll-like interleukin 1 receptor regulator is an important modulator of inflammation responsive genes," *Front. Immunol.*, vol. 10, no. FEB, 2019.
[38] R. Whelan, C. Kim, M. Chen, J. Leiter, M. M. Grunstein, and H. Hakonarson, "Role and regulation of interleukin-1 molecules in pro-asthmatic sensitised airway smooth muscle," *Eur. Respir. J.*, vol. 24, no. 4, pp. 559–567, Oct. 2004.
[39] K. R. Brown *et al.*, "Endotypes of difficult-to-control asthma in inner-city African American children.," *PLoS One*, vol. 12, no. 7, p. e0180778, 2017.
[40] J. Vanoevelen *et al.*, "The secretory pathway Ca2+/Mn2+-ATPase 2 is a Golgi-localized pump with high affinity for Ca2+ ions," *J. Biol. Chem.*, vol. 280, no. 24, pp. 22800–22808, Jun. 2005.
[41] D. K. Kim *et al.*, "Genome-Wide Association Analysis of Blood Biomarkers in Chronic Obstructive Pulmonary Disease," *Am. J. Respir. Crit. Care Med.*, vol. 186, no. 12, p. 1238, Dec. 2012.
[42] K. Voorhies *et al.*, "Age by single nucleotide polymorphism interactions on bronchodilator response in asthmatics," *J. Pers. Med.*, vol. 11, no. 1, pp. 1–9, Jan. 2021.

Tables

Table 1. Characteristics of the six cohorts included in the genome-wide association meta-analyses of bronchodilator response and the two pediatric cohorts used for validation analyses.

	Discovery Stage in Adult Cohorts								Validation in Pediatric Cohorts	
	European Ancestry						African Ancestry		European Ancestry	Hispanic/Latino
	FHS (N=1003)	COPDGene (N=6591)	ECLIPSE (N=1428)	GENKOLS (N=873)	TESRA (N=377)	SPIROMICS (N=1779)	COPDGene (N=3179)	SPIROMICS (N=418)	CAMP (N=570)	GACRS (N=979)
Age in years (SD)	57.9 (14.0)	65.1 (8.8)	62.7 (7.5)	59.7 (10.3)	66.6 (8.0)	65.2 (8.2)	54.7 (7.2)	58.5 (8.8)	8.92 ± 2.13	9.19 ± 1.88
Male (%)	486 (48%)	3442 (52%)	940 (66%)	507 (58%)	261 (69%)	993 (55.3%)	1774 (56%)	205 (48.8%)	340 (60%)	570 (58%)
BMI in kg/m^2 (SD)	27.7 (5.5)	28.7 (6.0)	26.9 (5.4)	26.0 (4.5)	25.9 (4.9)	27.8 (5.1)	29.1 (6.7)	27.9 (6.0)	NA	NA
Current Smoking (%)	120 (12%)	2582 (39%)	490 (34%)	398 (46%)	0 (0%)	598 (33.3%)	2544 (80%)	272 (64.8%)	NA	NA
Former Smoking (%)	511 (51%)	4009 (61%)	938 (66%)	475 (54%)	377 (100%)	1779 (100%)	635 (20%)	418 (100%)	NA	NA
Pack-years (SD)	25.3 (22.7)	47.3 (26.0)	47.4 (27.1)	25.3 (17.1)	45.9 (23.7)	52.2 (29.0)	38.3 (21.4)	41.2 (17.4)	NA	NA
Lung disease (%)										
Asthma	131 (13%)	1030 (16%)	244 (17%)	247 (28%)	NA***	300 (17.5%)	681 (21%)	130 (32.6%)	NA	NA
*COPD**	244 (24%)	2789 (42%)	1272 (89%)	443 (51%)	377 (100%)	982 (54.7%)	811 (26%)	183 (43.6%)	NA	NA
Pulmonary Function at Baseline										
*Baseline FEV1 as % predicted** (SD)*	87.4 (15.3)	70.0 (26.0)	51.2 (23.5)	69.5 (25.3)	46.30 (9.3)	65.2 (26.0)	79.0 (24.1)	70.0 (27.1)	95.0 (13.2)	99.7 (16.5)
Baseline FVC as % predicted (SD)	101.1 (15.6)	82.9 (18.8)	83.5 (21.8)	87.0 (17.3)	88.8 (17.3)	84.2 (19.2)	87.9 (19.2)	87.0 (21.1)	105.4 (12.6)	105.4 (16.0)
Baseline FEV1/FVC as % predicted (SD)	86.0 (8.0)	82.5 (20.6)	63.6 (18.9)	77.6 (19.1)	53.2 (10.8)	75.7 (2.1)	88.6 (16.5)	79.2 (1.8)	90.4 (8.8)	94.8 (8.3)
Baseline FEV1/FVC as % (SD)	67 (7)	63 (16)	48 (15)	64 (16)	42 (08)	56 (16)	70 (13)	62 (16)	80 (8)	84 (7)

Bronchodilator Response										
Change in FEV1 as % of baseline (SD)	5.3 (5.7)	6.3 (9.7)	9.5 (11.2)	5.8 (9.8)	7.9 (10.4)	13.2 (12.8)	4.4 (10.4)	10.8 (11.3)	9.7 (8.1)	4.9 (7.4)
Change in FVC as % of baseline (SD)	-0.02 (4.8)	4.5 (11.0)	8.5 (12.1)	2.9 (8.6)	6.2 (8.6)	8.8 (11.2)	2.3 (11.1)	6.9 (10.7)	1.8 (4.1)	1.3 (5.7)

	Discovery Stage in Adult Cohorts								**Validation in Pediatric Cohorts**	
	European Ancestry						**African Ancestry**		**European Ancestry**	**Hispanic/Latino**
	FHS (N=1003)	**COPDGene (N=6591)**	**ECLIPSE (N=1428)**	**GENKOLS (N=873)**	**TESRA (N=377)**	**SPIROMICS (N=1779)**	**COPDGene (N=3179)**	**SPIROMICS (N=418)**	**CAMP (N=570)**	**GACRS (N=979)**
Age in years (SD)	57.9 (14.0)	65.1 (8.8)	62.7 (7.5)	59.7 (10.3)	66.6 (8.0)	65.2 (8.2)	54.7 (7.2)	58.5 (8.8)	8.92 ± 2.13	9.19 ± 1.88
Male (%)	486 (48%)	3442 (52%)	940 (66%)	507 (58%)	261 (69%)	993 (55.3%)	1774 (56%)	205 (48.8%)	340 (60%)	570 (58%)
BMI in kg/m^2 (SD)	27.7 (5.5)	28.7 (6.0)	26.9 (5.4)	26.0 (4.5)	25.9 (4.9)	27.8 (5.1)	29.1 (6.7)	27.9 (6.0)	NA	NA
Current Smoking (%)	120 (12%)	2582 (39%)	490 (34%)	398 (46%)	0 (0%)	598 (33.3%)	2544 (80%)	272 (64.8%)	NA	NA
Former Smoking (%)	511 (51%)	4009 (61%)	938 (66%)	475 (54%)	377 (100%)	1779 (100%)	635 (20%)	418 (100%)	NA	NA
Pack-years (SD)	25.3 (22.7)	47.3 (26.0)	47.4 (27.1)	25.3 (17.1)	45.9 (23.7)	52.2 (29.0)	38.3 (21.4)	41.2 (17.4)	NA	NA
Lung disease (%)										
Asthma	131 (13%)	1030 (16%)	244 (17%)	247 (28%)	NA***	300 (17.5%)	681 (21%)	130 (32.6%)	NA	NA
*COPD**	244 (24%)	2789 (42%)	1272 (89%)	443 (51%)	377 (100%)	982 (54.7%)	811 (26%)	183 (43.6%)	NA	NA
Pulmonary Function at Baseline										

*Baseline FEV1 as % predicted** (SD)*	87.4 (15.3)	70.0 (26.0)	51.2 (23.5)	69.5 (25.3)	46.30 (9.3)	65.2 (26.0)	79.0 (24.1)	70.0 (27.1)	95.0 (13.2)	99.7 (16.5)
Baseline FVC as % predicted (SD)	101.1 (15.6)	82.9 (18.8)	83.5 (21.8)	87.0 (17.3)	88.8 (17.3)	84.2 (19.2)	87.9 (19.2)	87.0 (21.1)	105.4 (12.6)	105.4 (16.0)
Baseline FEV1/FVC as % predicted (SD)	86.0 (8.0)	82.5 (20.6)	63.6 (18.9)	77.6 (19.1)	53.2 (10.8)	75.7 (2.1)	88.6 (16.5)	79.2 (1.8)	90.4 (8.8)	94.8 (8.3)
Baseline FEV1/FVC as % (SD)	67 (7)	63 (16)	48 (15)	64 (16)	42 (08)	56 (16)	70 (13)	62 (16)	80 (8)	84 (7)
Bronchodilator Response										
Change in FEV1 as % of baseline (SD)	5.3 (5.7)	6.3 (9.7)	9.5 (11.2)	5.8 (9.8)	7.9 (10.4)	13.2 (12.8)	4.4 (10.4)	10.8 (11.3)	9.7 (8.1)	4.9 (7.4)
Change in FVC as % of baseline (SD)	-0.02 (4.8)	4.5 (11.0)	8.5 (12.1)	2.9 (8.6)	6.2 (8.6)	8.8 (11.2)	2.3 (11.1)	6.9 (10.7)	1.8 (4.1)	1.3 (5.7)

*COPD definition: FEV1/FVC<0.7 and FEV1 (% predicted)<0.8

~ percent predicted values are calculated using Hankinson equations

†TESRA cohort did not inclue participants with asthma

¶SPIROMICS: former smoker is defined as having at least a 20 pack-year history of smoking and inclusion criteria for SPIROMICS is a minimum of 20 pack-year smoking history

Cohort abbreviations: FHS=Framingham Hear Study; COPDGene= Genetic Epidemiology of COPD; ECLIPSE=Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; TESRA=Treatment of Emphysema with a Gamma-Selective Retinoid Agonist; GenKOLS=Bergen, Norway COPD Cohort; SPIROMICS= Subpopulations and Intermediate Outcome Measures in COPD Study

Table 2. Single nucleotide polymorphisms (SNPs) associated with bronchodilator response in six independent cohort meta-analysis with p-value<$5x10^{-6}$ after linkage disequilibrium-clumping in the ancestry-stratified meta-analysis and the combined meta-analysis.

	Anc/Phe[¶]	SNP	Chr:Position	Allele	AF*	Effect	SE	p-value	Closest Gene	Distance[†]
Ancestry-stratified meta-analysis	**EA FEV1**	rs13262811	8:142425325	A	0.85	0.81	0.17	1.8E-06	*PTP4A3*	6162
		rs140005306	2:143707656	A	0.95	1.25	0.26	2.0E-06	*KYNU*	within
		rs7315471	12:13333283	A	0.07	1.14	0.24	2.1E-06	*EMP1*	16318
		rs10220877	15:38934425	A	0.17	0.73	0.16	3.2E-06	*C15orf53*	54373
		rs76890972	16:84399755	A	0.09	1	0.22	4.7E-06	*ATP2C2*	2373
		rs72766398	2:12489567	T	0.95	1.31	0.28	3.6E-06	*MIR3681HG*	within
		rs8014708	14:101214590	A	0.1	-0.94	0.2	3.8E-06	*DLK1*	10029
	EA FVC	rs7096465	10:4250500	T	0.09	0.98	0.20	1.1E-06	*LINC00702*	within
		rs10894263	11:130699110	A	0.56	0.58	0.12	8.1E-07	*LOC100507431*	14977
		rs8046017	16:84378488	A	0.57	-0.56	0.12	4.3E-06	*WFDC1*	15031
		rs10020466	4:181306647	A	0.71	0.59	0.13	3.8E-06	*LINC00290*	678595
		rs989808	4:47166781	T	0.16	0.73	0.16	2.6E-06	*GABRB1*	within
	AA FEV1	rs116556600	21:15154158	A	0.43	-1.26	0.25	5.8E-07	*MIR8069-1*	57563
		rs11130868	3:6249417	C	0.6	1.2	0.24	9.8E-07	*GRM7-AS3*	424627
		rs35870000	9:14801710	A	0.12	-1.72	0.37	3.4E-06	*FREM1*	within
		rs2532841	10:119069842	A	0.66	1.16	0.25	4.8E-06	*PDZD8*	within
		rs4852100	2:240571827	A	0.76	-1.34	0.29	4.9E-06	*LOC150935*	112726
		rs58795512	2:40312398	A	0.94	-2.54	0.53	1.6E-06	*SLC8A1-AS1*	within
		rs491175	2:45151690	C	0.6	1.26	0.24	2.4E-07	*SIX3-AS1*	15602
		rs186201422	10:133458567	T	0.063	-2.85	0.62	3.7E-06	*N/A*	N/A
		rs144465006	11:18273453	A	0.077	-2.35	0.51	3.5E-06	*N/A*	N/A
		rs10426116	19:44591553	T	0.059	2.55	0.52	1.1E-06	*ZNF284*	within
	AA FVC	rs2400730	3:135796524	A	0.29	1.53	0.29	1.6E-07	*PPP2R3A*	within
		rs10495859	2:36241146	T	0.82	-1.77	0.34	2.0E-07	*LOC100288911*	340745

		rs12406488	1:88071848	A	0.87	-1.8	0.39	3.7E-06	*LINC01364*	234510
		rs11680558	2:11522391	A	0.086	2.68	0.56	1.4E-06	*LINC00570*	11715
		rs41265547	2:189872891	C	0.21	1.51	0.32	1.9E-06	*COL3A1*	within
		rs6864533	5:20534743	T	0.093	2.43	0.48	3.3E-07	*CDH18*	within
		rs1736601	6:167683260	T	0.64	1.24	0.27	3.5E-06	*UNC93A*	21542
		rs7336381	13:114963436	A	0.77	-1.42	0.31	3.4E-06	*CDC16*	36925
		rs80202087	15:78653983	A	0.095	-2.12	0.46	4.7E-06	*CRABP1*	13411
		rs1974858	16:26743681	A	0.42	-1.23	0.26	2.8E-06	*C16orf82*	334537
		rs3935851	8:31133902	T	0.1	2.41	0.52	3.1E-06	*WRN*	102625
		rs13437873	7:48189850	A	0.74	1.36	0.29	2.8E-06	*ABCA13*	21206
		rs2217516	8:94401023	A	0.57	1.24	0.26	1.6E-06	*LINC00535*	within
		rs12713765	2:72023225	A	0.59	1.27	0.25	6.4E-07	*DYSF*	109332
		rs113520112	2:110362336	C	0.093	2.24	0.44	3.5E-07	*SEPT10*	within
		rs74491400	2:224088691	T	0.062	2.49	0.53	2.4E-06	*KCNE4*	168334
		rs28672350	4:24166929	A	0.88	1.89	0.4	2.6E-06	*PPARGC1A*	275229
		rs55699229	8:19114322	T	0.9	-2.25	0.47	1.7E-06	*LOC100128993*	11290
		rs144212455	15:53363818	C	0.94	-2.59	0.54	1.9E-06	*ONECUT1*	281609
		rs199964754	18:63446314	T	0.51	1.42	0.3	2.4E-06	*CDH7*	within
Combined meta-analysis	**FEV1**	rs1953833	1:239941671	A	0.71	-0.54	0.12	3.6E-06	*CHRM3*	within
		rs140005306	2:143707656	A	0.95	1.20	0.26	3.0E-06	*KYNU*	within
		rs6780151	3:6249820	A	0.60	1.26	0.26	1.2E-06	*N/A*	N/A
		rs9868510	3:105700120	A	0.51	-0.52	0.11	2.1E-06	*CBLB*	112233
		rs9385215	6:122074667	A	0.10	-0.88	0.19	2.7E-06	*GJA1*	303777
		rs13262811	8:142425325	A	0.86	0.76	0.16	2.2E-06	*PTP4A3*	6162
		rs7079679	10:102055546	A	0.53	0.50	0.11	3.0E-06	*PKD2L1*	within
		rs186201422	10:133458567	T	0.06	-2.85	0.62	3.7E-06	*N/A*	N/A
		rs144465006	11:18273453	A	0.08	-2.35	0.51	3.5E-06	*N/A*	N/A

	rs11055267	12:13329855	A	0.93	-1.14	0.23	1.1E-06	*EMP1*	19746
	rs4782614	16:84396105	A	0.32	0.64	0.12	7.5E-08	*ATP2C2*	6023
	rs76890972	16:84399755	A	0.08	1.02	0.21	1.6E-06	*ATP2C2*	2373
	rs10426116	19:44591553	T	0.06	2.56	0.52	1.1E-06	*ZNF284*	within
FVC	rs113520112	2:110362336	C	0.09	2.24	0.44	3.6E-07	*SEPT10*	within
	rs73803631	4:24159527	A	0.91	2.08	0.45	4.5E-06	*PPARGC1A*	267827
	rs55699229	8:19114322	T	0.90	-2.25	0.47	1.7E-06	*N/A*	N/A
	rs75638212	10:22950466	T	0.86	-0.74	0.15	1.0E-06	*PIP4K2A*	within
	rs144212455	15:53363818	C	0.94	-2.59	0.54	1.9E-06	*ONECUT1*	281609
	rs4782614	16:84396105	A	0.32	0.57	0.12	2.5E-06	*ATP2C2*	6023
	rs71355331	18:45645902	T	0.94	1.12	0.24	3.6E-06	*ZBTB7C*	within
	rs199964754	18:63446314	T	0.51	1.42	0.30	2.4E-06	*CDH7*	within

¶: Ancestry/Phenotype
*EAF: effect allele frequency
†Distance: distance from closest gene measured in base pairs; “within” denotes SNPs that are located within the gene
Position: genome reference used hg19

Table 3. Single nucleotide polymorphisms (SNPs) with p-value<$5x10^{-6}$ and posterior probability greater than 70% after fine mapping using PAINTOR (Probabilistic Annotation INTegratOR) software

Ancestry/Phenotype	SNP	Chr:Position~	Allele	p-value	posterior probability	95% credible set	Closest Gene	Distance†
EA FEV1	rs13262811	8:142425325	A	1.8×10^{-6}	0.78	6	*PTP4A3*	6162
AA FEV1	rs35870000	9:14801710	A	3.4×10^{-6}	0.75	3	*FREM1*	within
	rs144465006	11:18273453	A	3.5×10^{-6}	0.79	8	*N/A*	N/A
	rs10426116	19:44591553	T	1.1×10^{-6}	0.73	6	*ZNF284*	within
AA FVC	rs11680558	2:11522391	A	1.4×10^{-6}	0.79	4	*LINC00570*	11715
	rs55699229	8:19114322	T	1.7×10^{-6}	0.93	2	*LOC100128993*	11290
	rs3935851	8:31133902	T	3.1×10^{-6}	0.88	4	*WRN*	102625

†Distance: distance from closest gene measured in base pairs; “within” denotes SNPs that are located within the gene
~Position: genome reference used hg19

Table 4. Single nucleopted polymorphysms (SNPs) from ancestry-stratified and combined meta-analyses with p<5×10-6 that with corresponding expression quantitative trait loci (eQTLs) in lung tissue and whole blood from the Genotype Tissue Expression (GTEx) Project

	Ancestry/Phenotype	SNP	Nearest Gene	GWAS p-value	Lung eQTL	WB eQTL
Ancestry-stratified meta-analysis	**EA FEV1**	rs13262811	*PTP4A3*	1.8E-06	*N/A*	*SLC45A4*
	EA FVC	rs7096465	*LINC00702*	1.1E-06	*LINC00702*	*N/A*
		rs7079903	*LINC00702*	1.1E-06	*LINC00702*	*N/A*
		rs11252396	*LINC00702*	1.4E-06	*LINC00702*	*N/A*
		rs7087175	*LINC00702*	2.9E-06	*LINC00702*	*N/A*
	AA FEV1	rs35870000	*FREM1*	3.4E-06	*N/A*	*RP11-408A13.4*
		rs2532841	*PDZD8*	4.8E-06	*PDZD8*	*PDZD8*
	AA FVC	rs7336381	*CDC16*	3.4E-06	*CDC16, UPF3A*	*CDC16*
		rs1736600	*UNC93A*	3.6E-06	*RP11-568A7.3*	*N/A*
		rs1757120	*UNC93A*	4.2E-06	*RP11-568A7.3*	*N/A*
Combined meta-analysis	**FEV1**	rs7079679	*PKD2L1*	3.0E-06	*CWF19L1, BLOC1S2*	*CWF19L1*
		rs13262811	*PTP4A3*	2.2E-06	*N/A*	*SLC45A4*
		rs4782614	*ATP2C2*	7.5E-08	*N/A*	*ATP2C2*
	FVC	rs4782614	*ATP2C2*	2.5E-06	*N/A*	*ATP2C2*

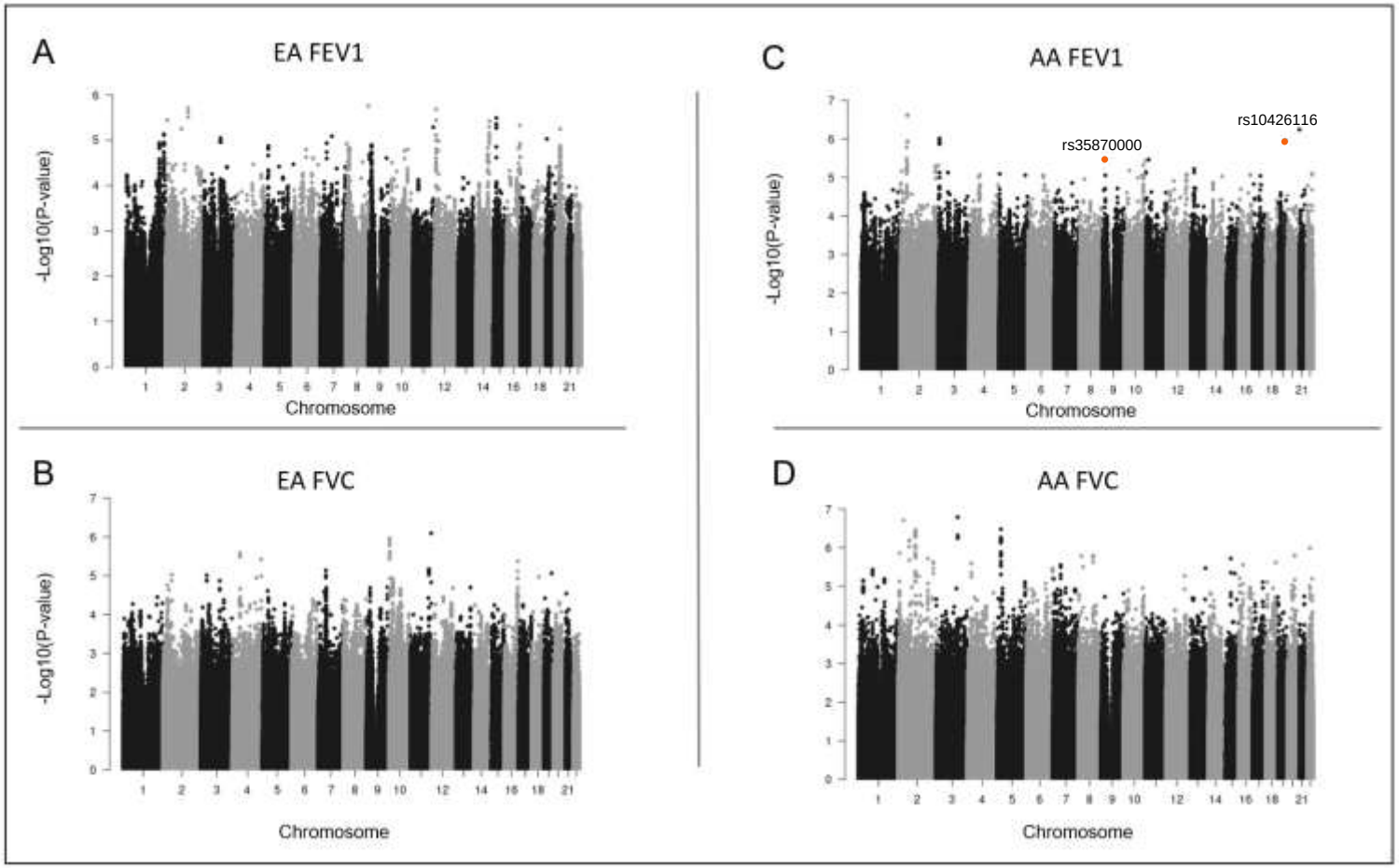

Figure 1. Plot of *P* values by chromosome for change in FEV1 and FVC in response to bronchodilator in the ancestry-stratified meta-analysis. Panels A-D denote the ancestry and phenotype: A) Change in FEV1 as percent predicted in European Ancestry (EA) participants. B) Change in FVC as percent predicted in EA participants. C) Change in FEV1 as percent predicted in African Ancestry (AA) participants. D) Change in FVC as percent predicted in AA participants.

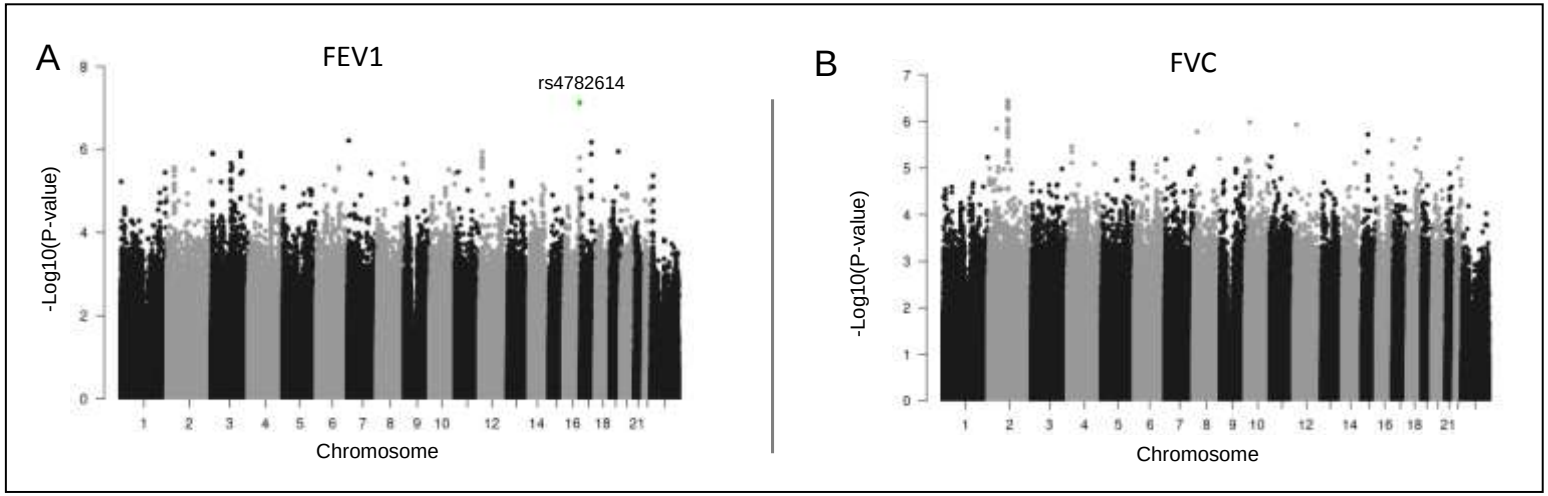

Figure 2. Plot of *P* values by chromosome for change in FEV1 and FVC in response to bronchodilator in the combined meta-analysis. Panel A) Change in FEV1 as percent predicted in European Ancestry (EA) and African Ancestry participants; Panel B) Change in FVC as percent predicted in EA and AA participants.

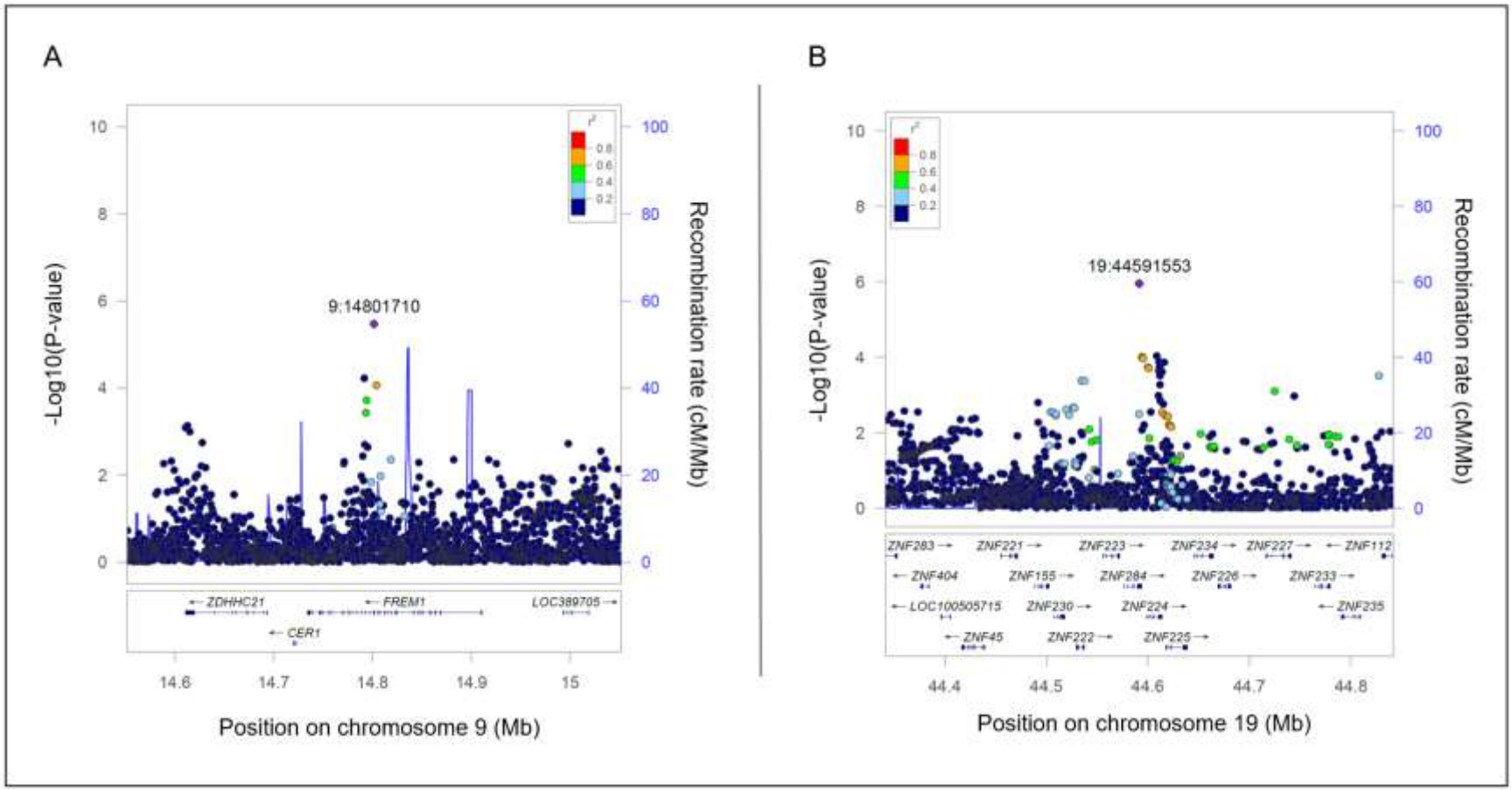

Figure 3. Regional and recombination plots near *FREM1* (Panel A) and *ZNF284* (Panel B)

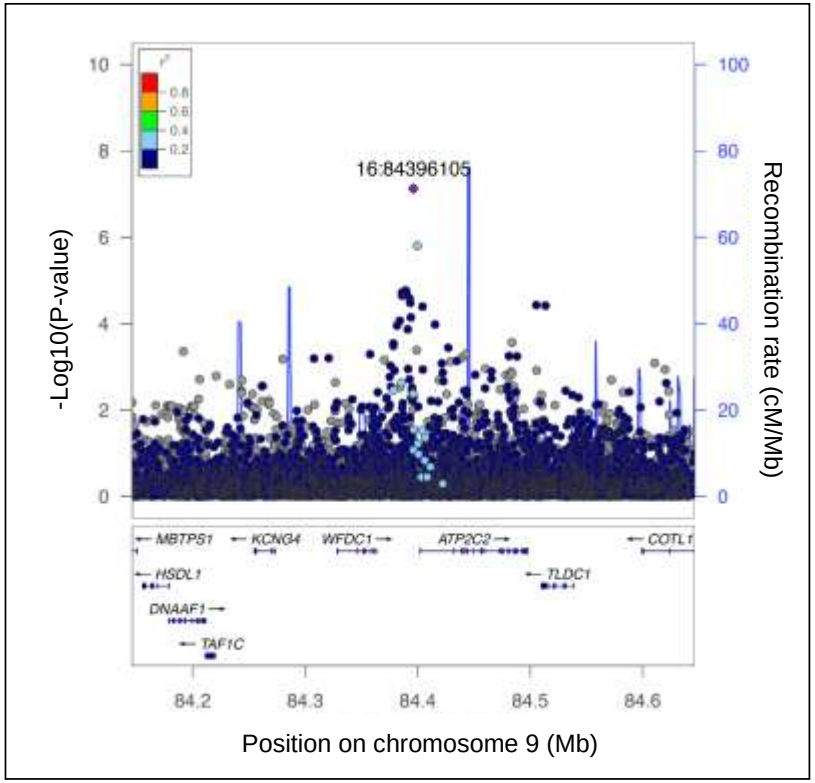

Figure 4. Regional and recombination plots near *ATP2C2*

Title: A genome-wide association study of bronchodilator response in multi-ancestry cohorts

Jessica D Gereige[1,2], Hanfei Xu[3], Victor E Ortega[4], Michael H Cho[5], Ming Liu[5,12], Phuwanat Sakornsakolpat[5], Edwin K Silverman[5], Terri H Beaty[6], Bruce E Miller[7], Per Bakke[8], Amund Gulsvik[8], Craig P Hersh[5], Jarrett D Morrow[5], International COPD Genetics Consortium, Elizabeth J Ampleford[4], Gregory A Hawkins[4], Eugene R Bleecker[4], Deborah A Meyers[4], Stephen P Peters[4], Juan C. Celedón[9], Kelan Tantisira[10], Jiang Li[5,11], Josée Dupuis[3], George T O'Connor[1,2]

Table of contents		**Pages**
Supplementary Tables		

Results

Descriptive Characteristics of Pediatric Cohorts

The baseline characteristics of the CAMP and GACRS participants in the analysis are shown in Table 1. A total of 570 participants of EA and 979 participants of Hispanic/Latino ethnicity were included in the validation analyses. The mean age of participants in the CAMP and GACRS cohorts was 8.92 years and 9.19 years respectively. The two cohorts were similar in their baseline pulmonary function, but the CAMP cohort had a larger change in FEV% from baseline in response to bronchodilators (9.78% in CAMP vs. 4.9% in GACRS).

Table S1. Details of single nucleotide polymorphism (SNP) genotyping, quality control (QC), imputation, and statistical analysis across cohorts

Study	Genotyping platform	QC filters for excluding genotyped SNPs	N, genotyped autosomal SNPs passing QC	Imputation software	Imputation Reference Panel	N, SNPs used for analysis	Statistical analysis software	Principal Components
FHS	Affymetrix 500K mapping array plus Affymetrix 50K supplemental array	call rate<97%,	412,049	University of Michigan	Haplotype Reference Consortium panel	40,084,637	lmekin, R	PC8
		HWE~ $P<10^{-6}$,		imputation server				
		MAF*<1%						
		Mendelian errors>=1000, or						
		At locations that did not map to GRCh37						
COPDGene	Illumina HumanOmniExpress array	missingness > 2%	797,983	University of Michigan	Haplotype Reference Consortium panel version 1.1	26,638,445	PLINK, R	EA: PC1-PC5; AA PC1-PC6
		MAF* < 1%		imputation server				

		deviation of Hardy–Weinberg at $P < 1 \times 10^{-5}$						
ECLIPSE	Human Hap550v3	missingness > 5%,	555,245	University of Michigan	Haplotype Reference Consortium panel version 1.1	19,918,371	PLINK, R	PC1-PC8
		monoallelic or singleton		imputation server				
		HWE~ $P<10^{-8}$						
GENKOLS	Human Hap550 V1,V3,DUO	missingness > 5%	520,275	University of Michigan	Haplotype Reference Consortium panel version 1.1	15,570,611	PLINK, R	PC1-PC14
		monoallelic or singleton		imputation server				
		HWE~ $P<10^{-8}$						
TESRA	Illumina	missingness > 1%	870,525	University of Michigan	Haplotype Reference Consortium panel version 1.1	15,554,092	PLINK, R	PC1-PC4
	HumanOmni1-Quad BeadChip	monoallelic		imputation server				
		HWE~ $P<1 \times 10^{-4}$						
SPIROMICS	Illumina HumanOmniExpressExome BeadChip and BeadStudio	call rate<97%	684,006	University of Michigan	Haplotype Reference Consortium panel version 1.1	26,403,168	PLINK	EA: PC7; AA: PC9
		HWE~ $P<10^{-6}$		imputation server				
		MAF*<1%						

*MAF: minor allele frequency
~HWE: Hardy-Weinberg equilibrium

Table S2. Single nucleotide polymorphisms (SNPs) with p-value<$5x10^{-6}$ associated with bronchodilator response in GWAS ancestry-stratified and combined meta-analyses of six independent cohorts

Ancestry-stratified meta-analysis							
Ancestry/Phenotype	**SNP**	**Chr:Position**	**Allele**	**AF**	**Effect**	**SE**	**p-value**
EA FEV1	rs72766398	2:12489567	T	0.95	1.31	0.28	3.6E-06
	rs149470223	2:143649430	A	0.94	1.24	0.26	2.4E-06
	rs74360662	2:143654379	T	0.06	-1.23	0.26	3.1E-06
	rs140005306	2:143707656	A	0.95	1.25	0.26	2.0E-06
	rs13262811	8:142425325	A	0.85	0.81	0.17	1.8E-06
	rs12228756	12:13326456	A	0.06	1.12	0.24	3.7E-06
	rs7315471	12:13333283	A	0.07	1.14	0.24	2.1E-06
	rs8014708	14:101214590	A	0.10	-0.94	0.20	3.8E-06
	rs17575173	15:38931954	A	0.17	0.72	0.16	4.6E-06
	rs10220877	15:38934425	A	0.17	0.73	0.16	3.2E-06
	rs4318178	15:38935041	T	0.17	0.72	0.16	4.4E-06
	rs76890972	16:84399755	A	0.09	1.00	0.22	4.7E-06
EA FVC	rs1542097	4:47161567	T	0.84	-0.73	0.16	3.2E-06
	rs988944	4:47163087	A	0.84	-0.73	0.16	3.2E-06
	rs989808	4:47166781	T	0.16	0.73	0.16	2.6E-06
	rs10020466	4:181306647	A	0.71	0.59	0.13	3.8E-06
	rs7087175	10:4248692	T	0.10	0.93	0.20	2.9E-06
	rs11815151	10:4248910	T	0.88	-0.86	0.18	2.4E-06
	rs11815129	10:4249061	A	0.88	-0.85	0.18	2.9E-06
	rs58150014	10:4249354	A	0.12	0.84	0.18	3.7E-06
	rs66719659	10:4249442	C	0.91	-0.98	0.20	1.7E-06
	rs7079903	10:4250410	A	0.91	-0.98	0.20	1.1E-06
	rs7096465	10:4250500	T	0.09	0.98	0.20	1.1E-06
	rs11252396	10:4253071	T	0.09	0.98	0.20	1.4E-06
	rs10894263	11:130699110	A	0.56	0.58	0.12	8.1E-07
	rs8046017	16:84378488	A	0.57	-0.56	0.12	4.3E-06
AA FEV1	rs75882995	2:40310460	A	0.94	-2.38	0.52	3.9E-06

	rs57791486	2:40311916	A	0.94	-2.46	0.53	3.3E-06
	rs58795512	2:40312398	A	0.94	-2.54	0.53	1.6E-06
	rs496467	2:45149003	T	0.61	1.13	0.25	4.8E-06
	rs517055	2:45150477	A	0.39	-1.18	0.24	1.2E-06
	rs486389	2:45151157	T	0.61	1.18	0.24	1.2E-06
	rs487260	2:45151242	A	0.39	-1.18	0.24	1.2E-06
	rs486917	2:45151441	A	0.60	1.26	0.24	2.5E-07
	rs485800	2:45151608	A	0.60	1.26	0.24	2.4E-07
	rs491175	2:45151690	C	0.60	1.26	0.24	2.4E-07
	rs4852100	2:240571827	A	0.76	-1.34	0.29	4.9E-06
	rs11130868	3:6249417	C	0.60	1.20	0.24	9.8E-07
	rs11130869	3:6249519	A	0.60	1.18	0.24	1.4E-06
	rs6768881	3:6249620	A	0.39	-1.20	0.25	1.0E-06
	rs6771552	3:6249703	T	0.39	-1.19	0.25	1.1E-06
	rs6771660	3:6249803	T	0.40	-1.26	0.26	1.3E-06
	rs6769069	3:6249806	A	0.40	-1.26	0.26	1.3E-06
	rs6780151	3:6249820	A	0.60	1.26	0.26	1.2E-06
	rs35870000	9:14801710	A	0.12	-1.72	0.37	3.4E-06
	rs2532841	10:119069842	A	0.66	1.16	0.25	4.8E-06
	rs186201422	10:133458567	T	0.06	-2.85	0.62	3.7E-06
	rs144465006	11:18273453	A	0.08	-2.35	0.51	3.5E-06
	rs10426116	19:44591553	T	0.06	2.56	0.52	1.1E-06
	rs116556600	21:15154158	A	0.43	-1.26	0.25	5.8E-07
AA FVC	rs12406488	1:88071848	A	0.87	-1.80	0.39	3.7E-06
	rs6701916	1:88077288	T	0.12	1.83	0.40	4.3E-06
	rs11680558	2:11522391	A	0.09	2.68	0.56	1.4E-06
	rs10495859	2:36241146	T	0.83	-1.77	0.34	2.0E-07
	rs2419777	2:72022087	T	0.40	-1.21	0.25	2.1E-06
	rs12623153	2:72022880	A	0.59	1.27	0.25	6.7E-07
	rs12713764	2:72023218	A	0.59	1.25	0.25	9.5E-07
	rs12713765	2:72023225	A	0.59	1.27	0.25	6.4E-07

rs113168856	2:110275743	A	0.11	1.87	0.41	4.3E-06
rs112287970	2:110277555	T	0.11	1.86	0.41	4.9E-06
rs113163585	2:110294414	T	0.10	1.99	0.42	1.8E-06
rs113163838	2:110312411	A	0.06	2.58	0.52	8.8E-07
rs28440810	2:110322704	C	0.06	2.57	0.52	9.3E-07
rs113307559	2:110323889	T	0.06	2.57	0.52	9.4E-07
rs111452745	2:110331092	T	0.09	2.17	0.43	5.0E-07
rs112462060	2:110346916	T	0.06	2.59	0.53	1.0E-06
rs111566351	2:110360671	A	0.91	-2.23	0.44	3.7E-07
rs112450144	2:110360823	A	0.09	2.20	0.44	5.3E-07
rs187889188	2:110361687	T	0.09	2.23	0.44	3.6E-07
rs113520112	2:110362336	C	0.09	2.24	0.44	3.5E-07
rs74868086	2:110373165	A	0.06	2.70	0.54	5.1E-07
rs76992194	2:110373468	A	0.94	-2.63	0.52	3.9E-07
rs113001438	2:110376483	C	0.94	-2.72	0.54	4.8E-07
rs111634292	2:110381056	A	0.06	2.74	0.54	4.6E-07
rs4953852	2:110383670	C	0.89	-2.01	0.42	1.7E-06
rs112520760	2:110383702	A	0.06	2.76	0.55	4.4E-07
rs111666992	2:110398852	A	0.94	-2.87	0.57	4.7E-07
rs59724818	2:110405235	T	0.93	-2.59	0.56	4.1E-06
rs114776525	2:110409387	A	0.06	2.84	0.59	1.7E-06
rs28636565	2:110410070	A	0.94	-2.84	0.59	1.6E-06
rs28626622	2:110413792	C	0.06	2.86	0.59	1.3E-06
rs28549324	2:110414161	T	0.06	2.84	0.59	1.7E-06
rs41265547	2:189872891	C	0.21	1.51	0.32	1.9E-06
rs11679475	2:224086699	A	0.94	-2.44	0.53	3.4E-06
rs74491400	2:224088691	T	0.06	2.49	0.53	2.4E-06
rs35240323	2:224092081	A	0.06	2.50	0.53	2.5E-06
rs10932997	2:224092667	A	0.94	-2.50	0.53	2.5E-06
rs12464171	2:224094460	A	0.94	-2.41	0.53	4.6E-06
rs58592880	3:135794742	A	0.29	1.46	0.29	4.8E-07

rs7623246	3:135795681	T	0.64	-1.39	0.28	5.7E-07
rs2400730	3:135796524	A	0.29	1.53	0.29	1.6E-07
rs73803631	4:24159527	A	0.91	2.08	0.45	4.5E-06
rs28672350	4:24166929	A	0.88	1.89	0.40	2.6E-06
rs60431648	5:20511040	T	0.09	2.33	0.49	1.7E-06
rs955747	5:20515561	T	0.09	2.37	0.49	1.5E-06
rs10462120	5:20516447	T	0.91	-2.38	0.48	7.5E-07
rs16886568	5:20518760	C	0.92	-2.36	0.50	3.0E-06
rs62355216	5:20519791	T	0.09	2.38	0.48	6.4E-07
rs12186433	5:20523710	T	0.09	2.38	0.48	6.6E-07
rs62352728	5:20529482	A	0.91	-2.38	0.48	6.3E-07
rs56232914	5:20529752	T	0.09	2.39	0.48	5.5E-07
rs12188294	5:20533514	A	0.88	-1.89	0.41	5.0E-06
rs6864533	5:20534743	T	0.09	2.43	0.48	3.3E-07
rs56306840	5:20535590	C	0.91	-2.42	0.49	6.5E-07
rs1366499	5:20536788	A	0.09	2.41	0.49	6.5E-07
rs62354276	5:20545310	T	0.09	2.36	0.49	1.3E-06
rs62354277	5:20545887	T	0.91	-2.28	0.49	2.8E-06
rs16886290	5:20548631	T	0.91	-2.35	0.49	1.5E-06
rs12514876	5:20552957	T	0.09	2.32	0.49	2.3E-06
rs1736599	6:167683244	A	0.64	1.24	0.27	3.6E-06
rs1736600	6:167683252	A	0.36	-1.24	0.27	3.6E-06
rs1736601	6:167683260	T	0.64	1.24	0.27	3.5E-06
rs1757120	6:167683392	T	0.64	1.22	0.27	4.2E-06
rs7458095	7:48176687	T	0.26	-1.33	0.29	5.0E-06
rs11769253	7:48183283	T	0.25	-1.35	0.29	3.2E-06
rs13437873	7:48189850	A	0.74	1.36	0.29	2.8E-06
rs7458844	7:48195351	A	0.25	-1.36	0.29	3.1E-06
rs55699229	8:19114322	T	0.90	-2.25	0.47	1.7E-06
rs3935851	8:31133902	T	0.10	2.41	0.52	3.1E-06
rs931476	8:94396331	C	0.57	1.24	0.26	1.8E-06

	rs11780241	8:94400744	A	0.43	-1.23	0.26	1.8E-06
	rs2217516	8:94401023	A	0.57	1.24	0.26	1.6E-06
	rs2217515	8:94404371	A	0.43	-1.20	0.25	2.4E-06
	rs7336381	13:114963436	A	0.77	-1.42	0.31	3.4E-06
	rs146129483	15:53344844	C	0.11	1.88	0.41	4.5E-06
	rs144212455	15:53363818	C	0.94	-2.59	0.54	1.9E-06
	rs80202087	15:78653983	A	0.10	-2.12	0.46	4.7E-06
	rs1974858	16:26743681	A	0.42	-1.23	0.26	2.8E-06
	rs199964754	18:63446314	T	0.51	1.42	0.30	2.4E-06
	rs73150065	20:47334279	T	0.08	2.27	0.47	1.6E-06
	rs61291953	20:47334520	C	0.08	2.27	0.47	1.6E-06
Combined Meta-Analysis							
Phenotype	**SNP**	**Chr:Position**	**Allele**	**AF**	**Effect**	**SE**	**p-value**
FEV1	rs1953833	1:239941671	A	0.71	-0.54	0.12	3.6E-06
	rs140005306	2:143707656	A	0.95	1.20	0.26	3.0E-06
	rs6771660	3:6249803	T	0.40	-1.26	0.26	1.3E-06
	rs6769069	3:6249806	A	0.40	-1.26	0.26	1.3E-06
	rs6780151	3:6249820	A	0.60	1.26	0.26	1.2E-06
	rs9868510	3:105700120	A	0.51	-0.52	0.11	2.1E-06
	rs9814261	3:105700717	T	0.49	0.51	0.11	3.2E-06
	rs9869772	3:105700732	C	0.51	-0.51	0.11	3.2E-06
	rs9387998	6:122074243	A	0.90	0.88	0.19	3.0E-06
	rs9385215	6:122074667	A	0.10	-0.88	0.19	2.7E-06
	rs13262811	8:142425325	A	0.86	0.76	0.16	2.2E-06
	rs7079679	10:102055546	A	0.53	0.50	0.11	3.0E-06
	rs186201422	10:133458567	T	0.06	-2.85	0.62	3.7E-06
	rs144465006	11:18273453	A	0.08	-2.35	0.51	3.5E-06
	rs11055259	12:13325209	A	0.94	-1.12	0.23	1.9E-06
	rs11055261	12:13325396	c	0.06	1.11	0.23	2.1E-06
	rs11055263	12:13327373	A	0.95	-1.13	0.24	2.7E-06

	rs11055266	12:13329382	T	0.06	1.13	0.23	1.6E-06
	rs74063255	12:13329613	A	0.06	1.07	0.23	2.5E-06
	rs11055267	12:13329855	A	0.93	-1.14	0.23	1.1E-06
	rs11055268	12:13330247	T	0.95	-1.13	0.24	1.9E-06
	rs11055270	12:13331931	T	0.05	1.18	0.25	1.5E-06
	rs4782614	16:84396105	A	0.32	0.64	0.12	7.5E-08
	rs76890972	16:84399755	A	0.08	1.02	0.21	1.6E-06
	rs10426116	19:44591553	T	0.06	2.56	0.52	1.1E-06
FVC	rs113168856	2:110275743	A	0.11	1.87	0.41	4.3E-06
	rs112287970	2:110277555	T	0.11	1.86	0.41	4.9E-06
	rs113163585	2:110294414	T	0.10	1.99	0.42	1.8E-06
	rs113163838	2:110312411	A	0.06	2.58	0.52	8.9E-07
	rs28440810	2:110322704	C	0.06	2.57	0.52	9.3E-07
	rs113307559	2:110323889	T	0.06	2.57	0.52	9.3E-07
	rs111452745	2:110331092	T	0.09	2.17	0.43	5.0E-07
	rs112462060	2:110346916	T	0.06	2.59	0.53	1.0E-06
	rs111566351	2:110360671	A	0.91	-2.23	0.44	3.7E-07
	rs112450144	2:110360823	A	0.09	2.20	0.44	5.3E-07
	rs187889188	2:110361687	T	0.09	2.23	0.44	3.6E-07
	rs113520112	2:110362336	C	0.09	2.24	0.44	3.6E-07
	rs74868086	2:110373165	A	0.06	2.70	0.54	5.1E-07
	rs76992194	2:110373468	A	0.94	-2.63	0.52	3.9E-07
	rs113001438	2:110376483	C	0.94	-2.72	0.54	4.8E-07
	rs111634292	2:110381056	A	0.06	2.74	0.54	4.6E-07
	rs112520760	2:110383702	A	0.06	2.76	0.55	4.4E-07
	rs111666992	2:110398852	A	0.94	-2.87	0.57	4.7E-07
	rs59724818	2:110405235	T	0.93	-2.59	0.56	4.2E-06
	rs114776525	2:110409387	A	0.06	2.84	0.59	1.7E-06
	rs28636565	2:110410070	A	0.94	-2.84	0.59	1.6E-06
	rs28626622	2:110413792	C	0.06	2.86	0.59	1.3E-06
	rs28549324	2:110414161	T	0.06	2.84	0.59	1.7E-06

rs7600969	2:110434663	T	0.06	2.02	0.43	2.2E-06
rs73803631	4:24159527	A	0.91	2.08	0.45	4.5E-06
rs55699229	8:19114322	T	0.90	-2.25	0.47	1.7E-06
rs75638212	10:22950466	T	0.86	-0.74	0.15	1.0E-06
rs146129483	15:53344844	C	0.11	1.88	0.41	4.5E-06
rs144212455	15:53363818	C	0.94	-2.59	0.54	1.9E-06
rs4782614	16:84396105	A	0.32	0.57	0.12	2.5E-06
rs71355331	18:45645902	T	0.94	1.12	0.24	3.6E-06
rs199964754	18:63446314	T	0.51	1.42	0.30	2.4E-06

Position: genome reference used hg19

Table S3. Validation of single nucleotide polymorphisms (SNPs) with p-value<$5x10^{-6}$ in the Genetics of Asthma in Costa Rica Study (GACRS) and the Childhood Asthma Management Program (CAMP) pediatric cohorts

			Meta-analysis stratified by ancestry					Validation in CAMP study (White sample)					Validation in GACRS (Hispanic sample)				
Ancestry/Phenotype	**SNP**	**Chr:Position**	**Allele**	**AF**	**Effect**	**SE**	**p-value**	**Allele**	**AF**	**Effect**	**SE**	**p-value**	**Allele**	**AF**	**Effect**	**SE**	**p-value**
EA FEV1	rs235921	1:171622871	C	0.02	1.96	0.43	5.3E-06	C	1.7E-02	0.61	1.82	0.74	C	7.2E-03	1.7E-02	2.0E-02	0.39
	rs71637436	1:172132909	C	0.98	-2.49	0.51	9.7E-07	G	1.5E-02	1.04	1.92	0.59	G	5.1E-03	7.0E-03	2.3E-02	0.76
	rs485412	1:239939896	T	0.75	-0.60	0.13	7.3E-06	C	2.3E-01	0.01	0.54	0.99	C	2.6E-01	-6.2E-03	3.8E-03	0.10
	rs1104370	1:239940177	A	0.75	-0.60	0.13	7.7E-06	G	2.3E-01	0.01	0.54	0.99	G	2.6E-01	-6.6E-03	3.8E-03	0.08
	rs72766398	2:12489567	T	0.95	1.31	0.28	3.6E-06	G	5.1E-02	1.20	1.05	0.25	G	2.5E-02	2.1E-04	1.1E-02	0.98
	rs115777171	2:101767347	A	0.07	1.16	0.26	5.6E-06	A	7.2E-02	-0.80	0.88	0.36	A	5.5E-02	3.1E-03	7.3E-03	0.67
	rs149470223	2:143649430	A	0.94	1.24	0.26	2.4E-06	G	5.3E-02	0.99	1.01	0.33	G	2.1E-02	-6.0E-03	1.2E-02	0.60
	rs74360662	2:143654379	T	0.06	-1.23	0.26	3.1E-06	T	5.3E-02	0.99	1.01	0.33	T	2.1E-02	-6.0E-03	1.2E-02	0.60
	rs140005306	2:143707656	A	0.95	1.25	0.26	2.0E-06	G	5.8E-02	-0.18	0.97	0.85	G	6.9E-02	-1.2E-03	6.6E-03	0.85
	rs73017427	2:168534638	T	0.99	3.09	0.67	4.1E-06	C	7.9E-03	-0.86	2.62	0.74	C	7.8E-02	-8.9E-03	6.1E-03	0.15
	rs138608601	3:10109060	C	0.99	-2.98	0.66	7.4E-06	G	3.5E-03	3.25	3.92	0.41	G	7.7E-03	2.7E-02	1.9E-02	0.15
	rs184476545	3:52030773	A	0.01	-2.75	0.57	1.3E-06	A	1.5E-02	0.98	1.92	0.61	A	5.1E-03	3.5E-02	2.3E-02	0.13
	rs138186682	3:69191402	A	0.99	-3.25	0.72	7.3E-06	G	6.1E-03	-4.10	2.96	0.17	G	1.4E-02	-1.3E-02	1.4E-02	0.33
	rs79924828	3:77687265	T	0.04	-1.55	0.34	6.3E-06	T	3.8E-02	1.87	1.26	0.14	T	8.2E-02	2.9E-03	5.9E-03	0.63
	rs9868510	3:105700120	A	0.56	-0.52	0.12	9.0E-06	C	4.4E-01	0.55	0.47	0.24	C	4.9E-01	6.9E-03	3.4E-03	0.05
	rs11973770	7:8788905	T	0.97	1.71	0.37	3.7E-06	G	2.4E-02	0.04	1.54	0.98	G	3.3E-02	-1.3E-02	8.9E-03	0.15
	rs541808372	7:40153241	C	0.01	2.88	0.64	7.4E-06	C	8.8E-03	-2.37	2.49	0.34	C	2.6E-03	-3.9E-02	3.3E-02	0.23
	rs1544442	7:70832556	T	0.12	0.87	0.20	8.2E-06	T	1.3E-01	0.27	0.69	0.70	T	1.3E-01	4.2E-03	4.8E-03	0.38
	rs76398170	8:49190912	A	0.97	1.74	0.37	3.2E-06	C	2.6E-02	-2.51	1.41	0.08	C	8.7E-03	-5.8E-03	1.8E-02	0.74

rs1425588	8:57581605	T	0.97	1.84	0.40	5.5E-06	G	2.1E-02	0.23	1.63	0.89	G	6.6E-03	-2.9E-03	2.0E-02	1.76E-02
rs13262811	8:142425325	A	0.85	0.81	0.17	1.8E-06	G	1.5E-01	0.08	0.64	0.90	G	2.0E-01	-9.7E-03	4.1E-03	0.89
rs10894263	11:130699110	A	0.56	0.54	0.12	5.2E-06	C	4.3E-01	0.16	0.47	0.73	C	4.1E-01	1.2E-05	3.3E-03	1.00
rs7967876	12:13324318	T	0.94	-1.09	0.24	7.9E-06	C	6.3E-02	-0.08	0.98	0.94	C	1.1E-01	-3.3E-04	5.2E-03	0.95
rs12228756	12:13326456	A	0.06	1.12	0.24	3.7E-06	A	6.2E-02	-0.02	0.98	0.99	A	1.0E-01	-2.0E-03	5.4E-03	0.71
rs11055270	12:13331931	T	0.05	1.17	0.26	7.7E-06	T	5.4E-02	-0.35	1.07	0.75	T	7.5E-02	-9.8E-04	6.2E-03	0.87
rs7315471	12:13333283	A	0.07	1.14	0.24	2.1E-06	A	6.3E-02	1.01	0.98	0.30	A	9.9E-02	-4.4E-04	5.5E-03	0.94
rs78665935	12:78461704	A	0.01	-2.31	0.51	6.5E-06	A	9.6E-03	0.54	2.38	0.82	A	1.5E-02	7.5E-03	1.4E-02	0.59
rs75156202	14:101205466	A	0.10	-0.88	0.20	8.5E-06	A	9.7E-02	0.02	0.80	0.98	A	7.6E-02	2.1E-03	6.4E-03	0.75
rs74819596	14:101207166	T	0.10	-0.89	0.20	7.3E-06	T	9.7E-02	0.02	0.80	0.98	T	7.6E-02	2.3E-03	6.4E-03	0.72
rs8014708	14:101214590	A	0.10	-0.94	0.20	3.8E-06	A	9.0E-02	0.24	0.82	0.77	A	7.6E-02	1.6E-03	6.4E-03	0.80
rs8017361	14:101218652	A	0.10	-0.90	0.20	5.1E-06	A	9.6E-02	0.24	0.81	0.77	A	7.7E-02	2.2E-03	6.4E-03	0.74
rs8017555	14:101218902	T	0.10	-0.89	0.20	7.0E-06	T	9.6E-02	0.26	0.80	0.75	T	7.7E-02	2.2E-03	6.4E-03	0.74
rs78437025	14:101237738	C	0.10	-0.90	0.20	8.7E-06	C	9.4E-02	0.15	0.80	0.85	C	7.5E-02	2.1E-03	6.4E-03	0.74
rs17236868	15:34648647	A	0.03	1.58	0.33	1.8E-06	A	3.4E-02	0.62	1.29	0.63	A	1.2E-02	-8.0E-03	1.4E-02	0.58
rs17575006	15:38928501	T	0.83	-0.71	0.16	5.4E-06	C	1.7E-01	-0.42	0.61	0.49	C	1.0E-01	7.0E-03	5.5E-03	0.20
rs17575173	15:38931954	A	0.17	0.72	0.16	4.6E-06	A	1.7E-01	-0.45	0.61	0.46	A	1.0E-01	7.0E-03	5.5E-03	0.20
rs10220877	15:38934425	A	0.17	0.73	0.16	3.2E-06	A	1.7E-01	-0.50	0.61	0.41	A	1.1E-01	2.5E-03	5.3E-03	0.63
rs4318178	15:38935041	T	0.17	0.72	0.16	4.4E-06	T	1.7E-01	-0.45	0.61	0.46	T	1.0E-01	7.0E-03	5.5E-03	0.20
rs72765739	15:92405987	T	0.01	-2.63	0.56	3.0E-06	T	1.8E-02	-2.14	1.73	0.22	T	5.1E-03	8.6E-04	2.3E-02	0.97
rs72751977	15:92473340	C	0.01	-2.48	0.55	6.4E-06	C	1.6E-02	-1.96	1.87	0.29	C	4.6E-03	-1.3E-02	2.5E-02	0.61
rs76890972	16:84399755	A	0.09	1.00	0.22	4.7E-06	A	7.8E-02	-0.63	0.88	0.47	A	6.2E-02	5.9E-03	7.0E-03	0.39
rs150011658	18:48942548	T	0.99	-2.62	0.59	7.9E-06	C	1.2E-02	0.39	2.11	0.85	C	4.6E-03	5.9E-04	2.4E-02	0.98
rs8108918	19:6854223	T	0.2	0.61	0.1	9.4E-06	T	2.7E-	0.05	0.5	0.93	T	2.7E-	5.9E-	3.8E-	0.88

				7		4			01		1			01	04	03	
	rs2424949	20:31676622	T	0.47	-0.53	0.12	5.7E-06	T	4.7E-01	0.50	0.45	0.26	T	4.8E-01	-2.2E-03	3.3E-03	0.50
	rs45470394	20:50307296	A	0.01	2.89	0.65	9.1E-06	A	3.5E-03	-5.61	3.90	0.15	A	1.0E-03	2.7E-02	5.2E-02	0.60
EA FVC	rs112023769	1:101916826	T	0.01	3.34	0.75	9.8E-06	T	1.1E-02	0.29	1.21	0.81	T	5.1E-04	-2.7E-02	5.7E-02	0.63
	rs141932336	1:101917569	A	0.01	4.02	0.82	9.9E-07	A	9.6E-03	0.85	1.26	0.50	A	5.1E-04	1.1E-02	5.7E-02	0.84
	rs116165378	2:56822632	T	0.94	1.15	0.26	9.4E-06	C	7.5E-02	-0.56	0.48	0.24	C	1.1E-02	-7.4E-03	1.2E-02	0.54
	rs62145108	2:71254735	T	0.99	-3.60	0.79	5.1E-06	G	6.1E-03	-1.35	1.58	0.39	G	5.1E-04	-1.2E-03	5.6E-02	0.98
	rs191169841	2:151168572	T	0.01	3.64	0.69	1.5E-07	T	4.4E-03	-0.36	2.17	0.87	T	4.6E-03	1.6E-02	1.9E-02	0.38
	rs143929696	2:151203874	T	0.01	3.66	0.78	2.9E-06	T	5.3E-03	-0.33	1.97	0.87	T	4.6E-03	1.6E-02	1.9E-02	0.38
	rs72889585	2:170575521	C	0.99	-2.78	0.62	6.6E-06	G	1.3E-02	-0.80	1.08	0.46	G	1.0E-02	-4.4E-04	1.3E-02	0.97
	rs11694059	2:170623550	C	0.01	2.78	0.62	7.6E-06	C	1.3E-02	-0.78	1.09	0.47	C	1.0E-02	4.1E-03	1.2E-02	0.74
	rs113711825	2:209074969	A	0.99	2.49	0.54	4.7E-06	C	8.8E-03	0.68	1.32	0.61	C	3.6E-03	6.4E-03	2.1E-02	0.77
	rs114658100	3:31164191	T	0.03	1.91	0.41	3.3E-06	T	2.6E-02	-0.52	0.78	0.50	T	7.2E-03	2.1E-02	1.5E-02	0.16
	rs7625563	3:34636234	A	0.84	0.70	0.16	9.8E-06	T	1.6E-01	-0.23	0.33	0.49	T	1.2E-01	-1.1E-03	4.0E-03	0.79
	rs3851381	3:168840607	T	0.97	1.56	0.34	3.9E-06	C	3.2E-02	1.18	0.72	0.10	C	1.1E-02	1.8E-03	1.2E-02	0.88
	rs142318979	3:178975772	A	0.99	-3.69	0.79	2.7E-06	G	9.6E-03	-1.17	1.15	0.31	G	2.0E-03	-2.2E-02	2.8E-02	0.44
	rs1542097	4:47161567	T	0.84	-0.73	0.16	3.2E-06	C	1.7E-01	-0.35	0.33	0.29	C	1.7E-01	4.2E-03	3.4E-03	0.23
	rs988944	4:47163087	A	0.84	-0.73	0.16	3.2E-06	G	1.7E-01	-0.35	0.33	0.29	G	1.7E-01	4.2E-03	3.4E-03	0.23
	rs989808	4:47166781	T	0.16	0.73	0.16	2.6E-06	T	1.7E-01	-0.35	0.33	0.29	T	1.7E-01	4.0E-03	3.4E-03	0.24
	rs116992081	4:121928275	T	0.01	2.84	0.64	9.2E-06	T	1.4E-02	0.21	1.06	0.84	T	2.0E-02	4.7E-03	9.1E-03	0.61
	rs10020466	4:181306647	A	0.71	0.59	0.13	3.8E-06	G	3.0E-01	0.49	0.26	0.06	G	2.3E-01	-5.1E-03	3.0E-03	0.10
	rs561454930	5:97985199	A	0.01	4.36	0.87	4.9E-07	A	8.8E-04	-3.96	4.14	0.34	A	5.1E-04	3.0E-02	5.6E-02	0.59
	rs186637189	5:98028962	A	0.01	4.52	0.87	2.1E-07	A	8.8E-04	-3.96	4.14	0.34	A	1.0E-03	1.5E-02	4.0E-02	0.71
	rs191498708	5:98091770	A	0.99	-4.54	0.88	2.6E-07	G	8.8E-04	-3.96	4.14	0.34	G	1.0E-03	1.5E-02	4.0E-02	0.71

rs6948083	7:46787500	A	0.46	0.52	0.12	9.8E-06	A	4.7E-01	-0.23	0.25	0.36	A	4.7E-01	4.1E-04	2.6E-03	0.88
rs6963868	7:46788710	T	0.54	-0.52	0.12	7.3E-06	G	4.7E-01	-0.18	0.24	0.47	G	4.7E-01	6.3E-04	2.6E-03	0.81
rs566387494	7:107335713	A	0.99	-5.57	1.17	2.1E-06	G	1.8E-03	-0.70	2.93	0.81	NA	NA	NA	NA	NA
rs191980579	7:107352211	A	0.01	5.62	1.17	1.6E-06	A	1.8E-03	-0.70	2.93	0.81	NA	NA	NA	NA	NA
rs117733370	7:107575605	T	0.99	-4.01	0.89	6.7E-06	C	2.6E-03	-0.95	2.40	0.69	C	5.1E-04	2.0E-02	5.7E-02	0.73
rs74483630	7:130415955	T	0.01	4.38	0.95	4.0E-06	T	3.5E-03	0.31	2.08	0.88	NA	NA	NA	NA	NA
rs117983031	8:205880	A	0.99	-3.96	0.84	2.5E-06	T	7.9E-03	-0.65	1.39	0.64	T	5.1E-04	7.5E-02	5.6E-02	0.18
rs117901373	8:92901670	T	0.99	-3.02	0.64	2.8E-06	C	7.0E-03	-0.77	1.47	0.60	C	2.9E-02	-5.8E-03	7.6E-03	0.45
rs145802738	8:93047122	A	0.01	3.72	0.75	7.9E-07	A	5.3E-03	-0.21	1.71	0.90	A	2.5E-02	-1.4E-02	7.9E-03	0.08
rs920874	8:93163126	T	0.01	3.12	0.68	4.8E-06	T	6.1E-03	-0.63	1.59	0.69	T	8.7E-02	-9.0E-03	4.5E-03	0.05
rs186942483	8:93168157	A	0.01	3.25	0.69	2.4E-06	A	7.0E-03	0.75	1.49	0.61	A	3.9E-02	-8.7E-03	6.4E-03	0.17
rs7087175	10:4248692	T	0.10	0.93	0.20	2.9E-06	T	8.5E-02	0.23	0.45	0.60	T	8.2E-02	2.7E-05	4.6E-03	1.00
rs11815151	10:4248910	T	0.88	-0.86	0.18	2.4E-06	C	1.1E-01	0.46	0.38	0.22	C	9.2E-02	-1.1E-03	4.4E-03	0.81
rs11815129	10:4249061	A	0.88	-0.85	0.18	2.9E-06	C	1.1E-01	0.46	0.38	0.22	C	9.1E-02	-8.3E-04	4.4E-03	0.85
rs58150014	10:4249354	A	0.12	0.84	0.18	3.7E-06	A	1.2E-01	0.44	0.38	0.25	A	9.8E-02	-4.2E-03	4.2E-03	0.32
rs66719659	10:4249442	C	0.91	-0.98	0.20	1.7E-06	G	8.4E-02	0.11	0.45	0.81	G	6.5E-02	5.3E-03	5.2E-03	0.30
rs7079903	10:4250410	A	0.91	-0.98	0.20	1.1E-06	T	8.3E-02	0.05	0.45	0.91	T	7.5E-02	3.9E-03	4.8E-03	0.42
rs7096465	10:4250500	T	0.09	0.98	0.20	1.1E-06	T	8.3E-02	0.05	0.45	0.91	T	7.4E-02	4.4E-03	4.8E-03	0.36
rs11252396	10:4253071	T	0.09	0.98	0.20	1.4E-06	T	8.3E-02	0.04	0.45	0.93	T	7.6E-02	3.5E-03	4.8E-03	0.46
rs188207742	11:31949453	A	0.01	5.31	1.05	4.0E-07	A	4.4E-03	1.98	1.85	0.29	NA	NA	NA	NA	NA
rs570448	11:116216432	C	0.16	-0.70	0.16	9.5E-06	C	1.6E-01	-0.33	0.35	0.35	C	1.2E-01	-4.9E-03	3.9E-03	0.21
rs568306	11:116223775	A	0.16	-0.70	0.16	7.2E-06	A	1.6E-01	-0.37	0.35	0.29	A	1.1E-01	-4.1E-03	4.0E-03	0.31
rs501755	11:116224621	T	0.16	-0.70	0.16	8.4E-06	T	1.6E-01	-0.37	0.35	0.29	T	1.2E-01	-3.2E-03	4.0E-03	0.42
rs577941	11:11622629	A	0.1	-0.71	0.1	6.8E-06	A	1.5E-	-0.36	0.3	0.31	A	1.1E-	-4.1E-	4.0E-	0.31

		0		6		6			01		6			01	03	03	
	rs564046	11:116226845	A	0.84	0.70	0.16	7.9E-06	G	1.5E-01	-0.28	0.35	0.43	G	1.1E-01	-4.1E-03	4.0E-03	0.31
	rs10894263	11:130699110	A	0.56	0.58	0.12	8.1E-07	C	4.3E-01	0.21	0.25	0.40	C	4.1E-01	-5.0E-04	2.6E-03	0.85
	rs56249492	12:81529421	A	0.99	-3.08	0.69	9.5E-06	G	8.8E-03	-1.00	1.32	0.45	NA	NA	NA	NA	NA
	rs61934751	12:81899927	T	0.99	-3.02	0.68	8.9E-06	C	6.1E-03	-1.11	1.57	0.48	NA	NA	NA	NA	NA
	rs536189804	12:113962880	T	0.01	5.19	1.06	1.0E-06	T	8.8E-04	-2.28	4.14	0.58	T	1.5E-03	3.9E-02	3.3E-02	0.24
	rs828207	13:91362390	T	0.99	-2.94	0.64	4.6E-06	C	5.3E-03	-1.32	1.70	0.44	C	1.2E-02	-6.7E-03	1.2E-02	0.58
	rs116931610	16:66527680	T	0.01	3.79	0.85	7.7E-06	T	6.1E-03	2.19	1.58	0.17	T	1.5E-03	5.1E-02	3.3E-02	0.12
	rs8046017	16:84378488	A	0.57	-0.56	0.12	4.3E-06	T	4.2E-01	0.09	0.25	0.72	A	5.0E-01	3.8E-04	2.5E-03	0.88
	rs9940576	16:84385389	C	0.54	0.53	0.12	7.7E-06	G	4.5E-01	-0.07	0.24	0.78	G	4.4E-01	3.6E-04	2.5E-03	0.89
	rs183161720	19:45383808	A	0.01	3.62	0.79	5.0E-06	A	9.6E-03	0.59	1.26	0.64	A	1.0E-03	-2.9E-02	4.0E-02	0.46
	rs11671612	19:48495128	T	0.33	-0.58	0.13	8.7E-06	T	3.3E-01	0.28	0.27	0.29	T	3.7E-01	5.1E-03	2.6E-03	0.05
	rs78093476	20:60223822	A	0.03	2.07	0.43	1.5E-06	A	1.6E-02	1.12	0.99	0.26	NA	NA	NA	NA	NA
	rs78766839	21:42206827	T	0.99	-3.49	0.77	6.0E-06	C	1.1E-02	-0.72	1.21	0.55	NA	NA	NA	NA	NA
	rs118019609	22:18527319	A	0.02	2.26	0.50	5.4E-06	A	1.8E-02	0.37	0.92	0.69	A	1.8E-02	2.2E-02	9.4E-03	0.02
	rs73394431	22:18528337	A	0.02	2.30	0.50	3.8E-06	A	1.8E-02	0.37	0.92	0.69	A	1.8E-02	2.2E-02	9.4E-03	0.02
	rs118068625	22:18529718	C	0.98	-2.33	0.50	2.9E-06	G	1.8E-02	0.37	0.92	0.69	G	1.8E-02	2.2E-02	9.4E-03	0.02
	rs143438884	22:18530010	T	0.02	2.34	0.50	2.8E-06	T	1.8E-02	0.37	0.92	0.69	T	1.8E-02	2.2E-02	9.4E-03	0.02
	rs5992977	22:18530144	T	0.02	2.19	0.49	8.0E-06	T	1.8E-02	0.37	0.92	0.69	T	2.7E-02	1.4E-02	7.9E-03	0.08
	rs5992978	22:18530208	A	0.02	2.20	0.49	6.8E-06	A	1.8E-02	0.37	0.92	0.69	A	2.7E-02	1.4E-02	7.9E-03	0.08
AA FEV1	rs35777690	2:8558126	T	0.88	1.93	0.43	6.8E-06	C	2.3E-01	0.08	0.56	0.88	C	1.9E-01	7.7E-03	4.2E-03	0.07
	rs73924751	2:40299633	T	0.06	2.29	0.51	8.0E-06	T	8.8E-04	21.66	7.74	0.01	T	4.6E-03	3.8E-02	2.4E-02	0.12
	rs143575150	2:40301971	A	0.06	2.32	0.51	6.5E-06	NA	NA	NA	NA	NA	A	4.6E-03	3.8E-02	2.4E-02	0.12
	rs57032634	2:40303534	T	0.94	-2.27	0.50	6.2E-06	C	8.8E-04	21.66	7.74	0.01	C	4.6E-03	3.8E-02	2.4E-02	0.12

rs60228195	2:40308204	T	0.06	2.33	0.51	5.4E-06	T	2.6E-03	4.30	4.50	0.34	T	4.6E-03	3.8E-02	2.4E-02	0.12
rs75882995	2:40310460	A	0.94	-2.38	0.52	3.9E-06	G	2.6E-03	4.30	4.50	0.34	G	4.6E-03	3.8E-02	2.4E-02	0.12
rs57791486	2:40311916	A	0.94	-2.46	0.53	3.3E-06	G	2.6E-03	4.30	4.50	0.34	G	4.6E-03	3.8E-02	2.4E-02	0.12
rs58795512	2:40312398	A	0.94	-2.54	0.53	1.6E-06	G	8.8E-04	21.66	7.74	0.01	G	4.6E-03	3.8E-02	2.4E-02	0.12
rs73924754	2:40315392	A	0.94	-2.30	0.51	5.9E-06	C	8.8E-04	21.66	7.74	0.01	C	4.6E-03	3.8E-02	2.4E-02	0.12
rs76641116	2:40319820	T	0.06	2.30	0.51	6.7E-06	NA	NA	NA	NA	NA	T	4.6E-03	3.8E-02	2.4E-02	0.12
rs496467	2:45149003	T	0.61	1.13	0.25	4.8E-06	T	2.1E-01	0.02	0.56	0.97	T	3.5E-01	-2.3E-03	3.4E-03	0.50
rs517055	2:45150477	A	0.39	-1.18	0.24	1.2E-06	T	2.1E-01	0.02	0.56	0.97	T	3.4E-01	-2.4E-03	3.4E-03	0.47
rs511704	2:45151055	T	0.37	-1.11	0.25	6.5E-06	C	2.1E-01	0.02	0.56	0.97	C	3.4E-01	-2.5E-03	3.4E-03	0.46
rs486389	2:45151157	T	0.61	1.18	0.24	1.2E-06	T	2.1E-01	0.02	0.56	0.97	T	3.4E-01	-2.4E-03	3.4E-03	0.47
rs487260	2:45151242	A	0.39	-1.18	0.24	1.2E-06	G	2.1E-01	0.02	0.56	0.97	G	3.4E-01	-2.4E-03	3.4E-03	0.47
rs486917	2:45151441	A	0.60	1.26	0.24	2.5E-07	A	2.1E-01	0.02	0.56	0.97	A	3.4E-01	-2.5E-03	3.4E-03	0.46
rs485800	2:45151608	A	0.60	1.26	0.24	2.4E-07	A	2.1E-01	0.02	0.56	0.97	A	3.4E-01	-2.7E-03	3.4E-03	0.43
rs491175	2:45151690	C	0.60	1.26	0.24	2.4E-07	C	2.1E-01	0.02	0.56	0.97	C	3.4E-01	-2.7E-03	3.4E-03	0.43
rs141801343	2:110880830	T	0.02	3.81	0.84	6.1E-06	NA	NA	NA	NA	NA	T	5.1E-04	-1.8E-02	7.3E-02	0.81
rs11679475	2:224086699	A	0.94	-2.27	0.50	5.0E-06	G	1.6E-01	0.57	0.65	0.38	G	1.0E-01	-9.8E-03	5.4E-03	0.07
rs74491400	2:224088691	T	0.06	2.26	0.50	6.3E-06	T	1.6E-01	0.58	0.64	0.37	T	1.0E-01	-9.8E-03	5.4E-03	0.07
rs35240323	2:224092081	A	0.06	2.26	0.50	7.1E-06	A	1.6E-01	0.58	0.64	0.37	A	1.0E-01	-9.8E-03	5.4E-03	0.07
rs10932997	2:224092667	A	0.94	-2.26	0.50	7.3E-06	T	1.6E-01	0.58	0.64	0.37	T	1.0E-01	-9.8E-03	5.4E-03	0.07
rs4852100	2:240571827	A	0.76	-1.34	0.29	4.9E-06	G	2.6E-01	0.09	0.53	0.87	G	4.6E-01	-2.3E-03	3.3E-03	0.49
rs11130868	3:6249417	C	0.60	1.20	0.24	9.8E-07	G	4.1E-01	-0.15	0.47	0.75	G	3.9E-01	-2.2E-03	3.3E-03	0.51
rs11130869	3:6249519	A	0.60	1.18	0.24	1.4E-06	C	4.1E-01	-0.14	0.47	0.77	C	3.9E-01	-2.2E-03	3.3E-03	0.51
rs6768881	3:6249620	A	0.39	-1.20	0.25	1.0E-06	A	4.0E-01	-0.29	0.48	0.54	A	3.8E-01	-3.2E-03	3.3E-03	0.33
rs6771552	3:6249703	T	0.3	-1.19	0.2	1.1E-06	T	4.0E-	-0.29	0.4	0.54	T	3.8E-	-3.3E-	3.3E-	0.32

			9		5			01		8			01	03	03	
	3:6249803	T	0.40	-1.26	0.26	1.3E-06	NA	NA	NA	NA	NA	T	3.8E-01	-3.3E-03	3.3E-03	0.32
	3:6249806	A	0.40	-1.26	0.26	1.3E-06	NA	NA	NA	NA	NA	A	3.8E-01	-3.3E-03	3.3E-03	0.32
	3:6249820	A	0.60	1.26	0.26	1.2E-06	NA	NA	NA	NA	NA	G	3.8E-01	-3.3E-03	3.3E-03	0.32
rs35663908	3:6253745	A	0.63	1.12	0.25	7.6E-06	G	4.2E-01	-0.06	0.47	0.89	G	3.8E-01	-2.2E-03	3.4E-03	0.51
rs13086424	3:59982062	T	0.30	1.19	0.27	7.5E-06	C	4.3E-01	0.45	0.48	0.35	T	4.5E-01	1.2E-03	3.2E-03	0.71
rs544921044	3:101732998	A	0.96	-2.70	0.60	7.2E-06	NA	NA	NA	NA	NA	G	2.6E-03	-6.5E-03	3.3E-02	0.84
rs79230295	3:101735651	A	0.04	2.71	0.60	5.7E-06	NA	NA	NA	NA	NA	A	2.6E-03	-6.5E-03	3.3E-02	0.84
rs113115805	4:58251056	A	0.80	-1.40	0.32	9.9E-06	T	4.4E-01	0.38	0.45	0.41	T	3.0E-01	5.4E-03	3.7E-03	0.14
	4:60553910	T	0.27	-1.28	0.29	9.6E-06	NA	NA	NA	NA	NA	T	1.4E-01	-6.4E-03	4.8E-03	0.18
rs111331192	4:65868514	T	0.13	1.61	0.36	8.6E-06	NA	NA	NA	NA	NA	T	5.6E-03	-1.5E-02	2.2E-02	0.50
	5:1061209	A	0.52	1.30	0.29	8.1E-06	NA	NA	NA	NA	NA	A	1.0E-01	-4.8E-03	5.4E-03	0.38
rs80031603	5:165486425	A	0.73	1.23	0.28	8.8E-06	G	5.8E-02	0.77	1.01	0.44	G	5.0E-02	1.4E-02	7.7E-03	0.07
	6:99653909	A	0.17	1.51	0.34	9.0E-06	NA	NA	NA	NA	NA	A	2.1E-01	2.1E-03	4.0E-03	0.61
	6:99654085	A	0.83	-1.51	0.34	8.8E-06	NA	NA	NA	NA	NA	C	2.1E-01	2.1E-03	4.0E-03	0.61
	6:99655935	T	0.18	1.50	0.34	9.1E-06	NA	NA	NA	NA	NA	T	2.1E-01	2.1E-03	4.0E-03	0.61
	6:99657859	T	0.83	-1.51	0.34	1.0E-05	NA	NA	NA	NA	NA	C	2.1E-01	2.3E-03	4.0E-03	0.57
rs2969021	7:2767135	A	0.98	-4.40	0.99	9.5E-06	T	1.0E-01	0.42	0.73	0.56	T	3.9E-02	1.3E-03	8.3E-03	0.88
	7:154002200	T	0.04	3.51	0.79	8.6E-06	NA	NA	NA	NA	NA	T	1.1E-02	1.2E-02	1.6E-02	0.44
rs7836839	8:8256178	C	0.96	2.71	0.60	7.6E-06	NA	NA	NA	NA	NA	G	2.0E-03	7.7E-02	3.7E-02	0.04
rs79385173	9:6484276	A	0.96	2.77	0.61	6.2E-06	NA	NA	NA	NA	NA	G	1.0E-02	5.8E-03	1.7E-02	0.73
rs28501137	9:6489641	C	0.04	-2.94	0.64	4.9E-06	NA	NA	NA	NA	NA	C	1.0E-02	5.8E-03	1.7E-02	0.73
rs35870000	9:14801710	A	0.12	-1.72	0.37	3.4E-06	A	3.4E-01	0.01	0.49	0.98	A	4.1E-01	2.3E-03	3.4E-03	0.50
rs10810945	9:18288212	T	0.07	-2.17	0.49	8.9E-06	T	3.6E-01	-0.29	0.49	0.55	T	2.3E-01	-9.3E-03	3.9E-03	0.02

rs116328566	9:82465310	A	0.97	-3.19	0.70	5.3E-06	NA	NA	NA	NA	NA	G	4.1E-03	2.7E-03	2.6E-02	0.92
rs74130168	10:30101477	T	0.09	-1.99	0.44	6.6E-06	T	4.4E-03	-1.56	3.50	0.66	T	3.1E-03	-5.7E-02	3.0E-02	0.06
rs79840959	10:30104089	T	0.04	-3.26	0.67	1.0E-06	NA	NA	NA	NA	NA	T	5.1E-04	8.7E-02	7.3E-02	0.24
rs2773207	10:109601892	A	0.90	-1.80	0.40	8.9E-06	G	6.8E-02	-0.17	0.91	0.85	G	7.2E-02	-5.8E-03	6.4E-03	0.37
rs2532841	10:119069842	A	0.66	1.16	0.25	4.8E-06	A	4.3E-01	-0.13	0.47	0.78	C	4.9E-01	6.1E-03	3.3E-03	0.06
rs12247698	10:119126650	T	0.33	-1.19	0.27	9.5E-06	C	4.4E-01	-0.10	0.47	0.82	T	4.9E-01	6.7E-03	3.3E-03	0.04
rs7087395	10:119127172	T	0.33	-1.20	0.27	9.1E-06	C	4.4E-01	-0.10	0.47	0.82	T	4.9E-01	6.8E-03	3.3E-03	0.04
rs1954213	10:119143950	T	0.34	-1.22	0.28	1.0E-05	C	4.3E-01	-0.14	0.47	0.77	C	5.0E-01	-5.5E-03	3.3E-03	0.10
	10:133458540	T	0.07	-2.48	0.55	6.8E-06	NA	NA	NA	NA	NA	T	1.2E-02	5.5E-03	1.5E-02	0.72
	10:133458567	T	0.06	-2.85	0.62	3.7E-06	NA	NA	NA	NA	NA	T	2.7E-02	-1.4E-03	1.0E-02	0.90
rs4047059	11:2038654	T	0.78	1.46	0.33	7.7E-06	C	1.3E-01	0.65	0.68	0.34	C	9.0E-02	-7.8E-03	5.8E-03	0.18
	11:18273453	A	0.08	-2.35	0.51	3.5E-06	NA	NA	NA	NA	NA	A	7.2E-03	-2.9E-02	2.0E-02	0.14
rs73409301	12:125150317	A	0.15	1.48	0.33	8.6E-06	A	9.0E-02	-0.44	0.80	0.59	A	9.3E-02	6.2E-03	5.6E-03	0.27
rs73409302	12:125150325	A	0.15	1.48	0.33	8.4E-06	A	9.0E-02	-0.44	0.80	0.59	A	9.3E-02	6.2E-03	5.6E-03	0.27
rs56052610	12:125151119	A	0.81	-1.38	0.31	8.6E-06	G	1.2E-01	0.21	0.71	0.77	G	1.5E-01	7.0E-04	4.5E-03	0.88
rs7132377	12:125151994	A	0.15	1.47	0.33	9.0E-06	A	9.1E-02	-0.43	0.79	0.58	A	9.3E-02	6.2E-03	5.6E-03	0.27
rs76290507	13:39485022	T	0.06	2.28	0.50	6.0E-06	NA	NA	NA	NA	NA	T	3.1E-03	-4.4E-02	3.0E-02	0.14
rs75550240	13:39522948	T	0.06	2.29	0.51	7.4E-06	NA	NA	NA	NA	NA	T	3.1E-03	-4.4E-02	3.0E-02	0.14
rs116454257	14:103293312	C	0.84	1.51	0.34	9.4E-06	G	1.8E-03	-1.19	5.51	0.83	G	1.1E-02	-6.3E-03	1.5E-02	0.68
rs75939142	16:73133159	A	0.09	1.91	0.43	8.6E-06	NA	NA	NA	NA	NA	A	6.6E-03	-9.0E-03	2.0E-02	0.66
rs76204966	16:73135149	T	0.91	-1.91	0.43	8.7E-06	NA	NA	NA	NA	NA	C	6.6E-03	-9.0E-03	2.0E-02	0.66
rs11657639	17:46547464	A	0.48	-1.11	0.25	9.2E-06	G	4.1E-01	-0.60	0.47	0.20	A	4.9E-01	2.4E-03	3.4E-03	0.47
rs1943433	18:64553825	T	0.98	-3.73	0.83	7.5E-06	C	8.8E-04	2.45	7.82	0.75	C	1.9E-02	-1.4E-02	1.2E-02	0.25
rs10426116	19:44591553	T	0.0	2.56	0.5	1.1E-06	NA	NA	NA	NA	NA	T	1.0E-	6.0E-	5.2E-	0.25

				6		2								03	02	02	
	rs79815297	20:15538607	T	0.03	3.68	0.82	7.8E-06	NA	NA	NA	NA	NA	T	1.5E-03	4.2E-02	4.2E-02	0.32
	rs116556600	21:15154158	A	0.43	-1.26	0.25	5.8E-07	A	1.8E-03	16.36	5.48	2.95E-03	NA	NA	NA	NA	NA
	rs79837253	22:47561065	A	0.06	2.35	0.53	7.9E-06	NA	NA	NA	NA	NA	A	6.6E-03	1.8E-02	2.0E-02	0.39
		22:47561184	T	0.97	-4.42	0.88	5.8E-07	NA	NA	NA	NA	NA	G	3.6E-03	2.1E-02	2.8E-02	0.46
		22:47561191	A	0.97	-4.60	0.87	1.1E-07	NA	NA	NA	NA	NA	G	3.6E-03	2.1E-02	2.8E-02	0.46
	rs148151878	22:47561214	A	0.95	-2.55	0.57	8.6E-06	NA	NA	NA	NA	NA	G	6.1E-03	3.0E-03	2.1E-02	0.89
AA FVC	rs11247742	1:28379130	T	0.37	-1.17	0.26	7.2E-06	T	2.9E-01	0.36	0.27	0.19	T	3.3E-01	1.3E-03	2.8E-03	0.64
	rs6661800	1:28380087	A	0.37	-1.17	0.26	7.3E-06	A	2.9E-01	0.36	0.27	0.19	A	3.3E-01	1.3E-03	2.8E-03	0.64
	rs12406488	1:88071848	A	0.87	-1.80	0.39	3.7E-06	T	4.7E-01	0.09	0.26	0.71	T	3.7E-01	-1.6E-03	2.6E-03	0.55
	rs6701916	1:88077288	T	0.12	1.83	0.40	4.3E-06	T	4.5E-01	0.11	0.26	0.65	T	3.5E-01	-2.1E-03	2.7E-03	0.43
	rs726300	1:88103212	A	0.87	-1.83	0.40	5.1E-06	G	4.6E-01	0.12	0.25	0.65	G	3.5E-01	-2.8E-03	2.7E-03	0.31
	rs2842004	1:162982502	T	0.27	1.33	0.30	8.0E-06	T	2.3E-01	0.60	0.30	0.04	T	2.7E-01	-5.7E-04	2.8E-03	0.84
	rs1507745	1:162989647	A	0.74	-1.32	0.29	6.5E-06	C	2.4E-01	0.56	0.29	0.05	C	2.7E-01	-3.6E-04	2.9E-03	0.90
	rs1507746	1:162995355	A	0.26	1.30	0.29	6.9E-06	A	2.3E-01	0.60	0.30	0.04	A	2.7E-01	3.3E-05	2.9E-03	0.99
	rs78968854	2:9495193	T	0.12	1.74	0.39	7.5E-06	T	8.8E-04	0.62	4.19	0.88	T	3.2E-02	5.7E-03	7.3E-03	0.44
	rs11680558	2:11522391	A	0.09	2.68	0.56	1.4E-06	A	1.8E-01	0.08	0.31	0.79	A	1.7E-01	-4.6E-04	3.4E-03	0.89
	rs10495859	2:36241146	T	0.83	-1.77	0.34	2.0E-07	C	1.4E-01	0.71	0.35	0.04	C	1.0E-01	1.1E-03	4.2E-03	0.79
	rs145021672	2:44341129	T	0.02	4.08	0.92	8.6E-06	NA	NA	NA	NA	NA	T	1.0E-03	2.4E-02	4.0E-02	0.54
	rs115430392	2:60068139	T	0.02	3.87	0.87	9.0E-06	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	rs2419777	2:72022087	T	0.40	-1.21	0.25	2.1E-06	C	4.3E-01	0.53	0.25	0.03	T	4.7E-01	5.5E-03	2.5E-03	0.03
	rs12623153	2:72022880	A	0.59	1.27	0.25	6.7E-07	A	4.3E-01	0.54	0.24	0.03	G	4.7E-01	5.4E-03	2.5E-03	0.03
	rs12713764	2:72023218	A	0.59	1.25	0.25	9.5E-07	A	4.3E-01	0.54	0.24	0.03	G	4.7E-01	5.4E-03	2.5E-03	0.03
	rs12713765	2:72023225	A	0.59	1.27	0.25	6.4E-07	A	4.3E-01	0.54	0.24	0.03	G	4.7E-01	5.4E-03	2.5E-03	0.03

rs113168856	2:110275743	A	0.11	1.87	0.41	4.3E-06	A	8.8E-04	2.87	4.14	0.49	A	1.2E-02	-1.0E-02	1.2E-02	0.37
rs112287970	2:110277555	T	0.11	1.86	0.41	4.9E-06	T	8.8E-04	2.87	4.14	0.49	T	1.2E-02	-1.0E-02	1.2E-02	0.37
rs113418271	2:110278325	C	0.89	-1.85	0.41	5.4E-06	G	8.8E-04	2.87	4.14	0.49	G	1.2E-02	-1.0E-02	1.2E-02	0.37
rs181353031	2:110278766	T	0.11	1.85	0.41	5.6E-06	T	8.8E-04	2.87	4.14	0.49	T	1.3E-02	-1.2E-02	1.1E-02	0.28
rs112819481	2:110281486	A	0.11	1.82	0.41	7.5E-06	A	8.8E-04	2.87	4.14	0.49	A	1.3E-02	-1.2E-02	1.1E-02	0.28
rs113163585	2:110294414	T	0.10	1.99	0.42	1.8E-06	T	8.8E-04	2.87	4.14	0.49	T	1.5E-02	-2.1E-03	1.0E-02	0.84
rs78150331	2:110298755	A	0.07	2.24	0.50	7.6E-06	A	8.8E-04	2.87	4.14	0.49	A	1.1E-02	-2.9E-03	1.2E-02	0.81
rs113163838	2:110312411	A	0.06	2.58	0.52	8.8E-07	A	8.8E-04	2.87	4.14	0.49	A	7.7E-03	-1.1E-02	1.5E-02	0.44
rs28440810	2:110322704	C	0.06	2.57	0.52	9.3E-07	C	8.8E-04	2.87	4.14	0.49	C	7.2E-03	-9.8E-03	1.5E-02	0.52
rs113307559	2:110323889	T	0.06	2.57	0.52	9.4E-07	T	8.8E-04	2.87	4.14	0.49	T	7.2E-03	-9.8E-03	1.5E-02	0.52
rs113794292	2:110328358	C	0.07	2.23	0.50	7.7E-06	C	8.8E-04	2.87	4.14	0.49	C	9.7E-03	-9.5E-04	1.3E-02	0.94
rs111452745	2:110331092	T	0.09	2.17	0.43	5.0E-07	T	8.8E-04	2.87	4.14	0.49	T	1.2E-02	-5.3E-03	1.2E-02	0.65
rs112462060	2:110346916	T	0.06	2.59	0.53	1.0E-06	T	8.8E-04	2.87	4.14	0.49	T	7.2E-03	-9.8E-03	1.5E-02	0.52
rs111566351	2:110360671	A	0.91	-2.23	0.44	3.7E-07	T	8.8E-04	2.87	4.14	0.49	T	1.1E-02	-9.3E-03	1.2E-02	0.44
rs112450144	2:110360823	A	0.09	2.20	0.44	5.3E-07	A	3.5E-03	1.46	2.08	0.48	A	1.2E-02	-9.0E-03	1.2E-02	0.44
rs187889188	2:110361687	T	0.09	2.23	0.44	3.6E-07	T	8.8E-04	2.87	4.14	0.49	T	1.1E-02	-9.3E-03	1.2E-02	0.44
rs113520112	2:110362336	C	0.09	2.24	0.44	3.5E-07	C	8.8E-04	2.87	4.14	0.49	C	1.1E-02	-9.3E-03	1.2E-02	0.44
rs74868086	2:110373165	A	0.06	2.70	0.54	5.1E-07	A	8.8E-04	2.87	4.14	0.49	A	6.1E-03	-9.3E-03	1.6E-02	0.57
rs76992194	2:110373468	A	0.94	-2.63	0.52	3.9E-07	G	8.8E-04	2.87	4.14	0.49	G	6.1E-03	-9.3E-03	1.6E-02	0.57
rs113001438	2:110376483	C	0.94	-2.72	0.54	4.8E-07	G	8.8E-04	2.87	4.14	0.49	G	6.1E-03	-9.3E-03	1.6E-02	0.57
rs111634292	2:110381056	A	0.06	2.74	0.54	4.6E-07	A	8.8E-04	2.87	4.14	0.49	A	6.1E-03	-9.3E-03	1.6E-02	0.57
rs4953852	2:110383670	C	0.89	-2.01	0.42	1.7E-06	G	3.9E-02	1.20	0.60	0.05	G	5.0E-02	-6.3E-03	5.8E-03	0.28
rs112520760	2:110383702	A	0.06	2.76	0.55	4.4E-07	A	8.8E-04	2.87	4.14	0.49	A	6.1E-03	-9.3E-03	1.6E-02	0.57
rs11166699	2:110398852	A	0.9	-2.87	0.5	4.7E-07	T	8.8E-	2.87	4.1	0.49	T	6.1E-	-9.3E-	1.6E-	0.57

2			4		7			04		4			03	03	02	
rs59724818	2:110405235	T	0.93	-2.59	0.56	4.1E-06	G	8.8E-04	2.87	4.14	0.49	G	5.6E-03	-1.2E-02	1.7E-02	0.47
rs114776525	2:110409387	A	0.06	2.84	0.59	1.7E-06	A	8.8E-04	2.87	4.14	0.49	A	2.6E-03	-1.6E-02	2.5E-02	0.54
rs28636565	2:110410070	A	0.94	-2.84	0.59	1.6E-06	G	8.8E-04	2.87	4.14	0.49	G	2.6E-03	-1.6E-02	2.5E-02	0.54
rs28626622	2:110413792	c	0.06	2.86	0.59	1.3E-06	C	8.8E-04	2.87	4.14	0.49	C	2.6E-03	-1.6E-02	2.5E-02	0.54
rs28549324	2:110414161	T	0.06	2.84	0.59	1.7E-06	T	8.8E-04	2.87	4.14	0.49	T	2.6E-03	-1.6E-02	2.5E-02	0.54
rs4850201	2:132178191	T	0.28	1.32	0.29	5.5E-06	T	2.1E-01	0.40	0.28	0.16	T	4.3E-01	4.9E-04	2.5E-03	0.85
rs41265547	2:189872891	C	0.21	1.51	0.32	1.9E-06	C	7.0E-03	2.57	1.47	0.08	C	1.7E-02	-3.2E-03	1.0E-02	0.75
rs16831014	2:189879285	A	0.19	1.46	0.33	8.5E-06	A	8.8E-04	15.04	4.09	0.00	A	1.0E-02	-7.2E-03	1.3E-02	0.57
rs11679475	2:224086699	A	0.94	-2.44	0.53	3.4E-06	G	1.6E-01	0.32	0.34	0.35	G	1.0E-01	-1.3E-03	4.2E-03	0.75
rs74491400	2:224088691	T	0.06	2.49	0.53	2.4E-06	T	1.6E-01	0.39	0.34	0.26	T	1.0E-01	-1.3E-03	4.2E-03	0.75
rs35240323	2:224092081	A	0.06	2.50	0.53	2.5E-06	A	1.6E-01	0.39	0.34	0.26	A	1.0E-01	-1.3E-03	4.2E-03	0.75
rs10932997	2:224092667	A	0.94	-2.50	0.53	2.5E-06	T	1.6E-01	0.39	0.34	0.26	T	1.0E-01	-1.3E-03	4.2E-03	0.75
rs12464171	2:224094460	A	0.94	-2.41	0.53	4.6E-06	C	1.6E-01	0.39	0.34	0.26	NA	NA	NA	NA	NA
.	3:135794742	A	0.29	1.46	0.29	4.8E-07	A	8.2E-02	0.81	0.46	0.08	A	5.2E-02	1.1E-02	5.5E-03	0.05
rs7623246	3:135795681	T	0.64	-1.39	0.28	5.7E-07	C	8.2E-02	0.81	0.46	0.08	C	5.8E-02	9.1E-03	5.2E-03	0.08
rs2400730	3:135796524	A	0.29	1.53	0.29	1.6E-07	A	8.2E-02	0.81	0.46	0.08	A	5.3E-02	1.0E-02	5.5E-03	0.07
rs73803631	4:24159527	A	0.91	2.08	0.45	4.5E-06	C	8.8E-04	-2.72	4.14	0.51	C	5.1E-03	-6.9E-03	1.8E-02	0.70
rs28672350	4:24166929	A	0.88	1.89	0.40	2.6E-06	G	1.8E-03	-2.07	2.93	0.48	G	2.0E-02	4.3E-03	9.2E-03	0.64
rs10032648	4:24169372	T	0.88	1.82	0.40	5.7E-06	G	1.8E-03	-2.07	2.93	0.48	G	2.0E-02	4.3E-03	9.2E-03	0.64
rs60431648	5:20511040	T	0.09	2.33	0.49	1.7E-06	T	1.9E-01	-0.12	0.32	0.71	T	3.4E-01	5.1E-03	2.6E-03	0.05
rs955747	5:20515561	T	0.09	2.37	0.49	1.5E-06	T	1.9E-01	-0.15	0.32	0.64	T	3.4E-01	5.0E-03	2.6E-03	0.06
rs10462120	5:20516447	T	0.91	-2.38	0.48	7.5E-07	C	1.9E-01	-0.15	0.32	0.64	C	3.4E-01	5.1E-03	2.6E-03	0.05
rs16886568	5:20518760	C	0.92	-2.36	0.50	3.0E-06	G	1.7E-01	-0.03	0.33	0.94	G	3.3E-01	4.9E-03	2.6E-03	0.06

rs62355216	5:20519791	T	0.09	2.38	0.48	6.4E-07	T	1.9E-01	-0.15	0.32	0.64	T	3.4E-01	5.1E-03	2.6E-03	0.05
rs12186433	5:20523710	T	0.09	2.38	0.48	6.6E-07	T	1.9E-01	-0.15	0.32	0.64	T	3.4E-01	4.1E-03	2.6E-03	0.12
rs62352728	5:20529482	A	0.91	-2.38	0.48	6.3E-07	C	1.9E-01	-0.15	0.32	0.64	C	3.4E-01	3.8E-03	2.6E-03	0.15
rs56232914	5:20529752	T	0.09	2.39	0.48	5.5E-07	T	1.9E-01	-0.15	0.32	0.64	T	3.4E-01	3.8E-03	2.6E-03	0.15
rs12188294	5:20533514	A	0.88	-1.89	0.41	5.0E-06	C	1.9E-01	-0.17	0.32	0.60	C	3.4E-01	3.6E-03	2.6E-03	0.17
rs6864533	5:20534743	T	0.09	2.43	0.48	3.3E-07	T	1.8E-01	-0.16	0.32	0.62	T	3.4E-01	3.7E-03	2.6E-03	0.16
rs56306840	5:20535590	c	0.91	-2.42	0.49	6.5E-07	G	1.8E-01	-0.16	0.32	0.62	G	3.4E-01	3.5E-03	2.6E-03	0.18
rs1366499	5:20536788	A	0.09	2.41	0.49	6.5E-07	A	1.8E-01	-0.16	0.32	0.62	A	3.4E-01	3.5E-03	2.6E-03	0.18
rs62354276	5:20545310	T	0.09	2.36	0.49	1.3E-06	T	1.9E-01	-0.15	0.32	0.64	T	3.4E-01	3.6E-03	2.6E-03	0.17
rs62354277	5:20545887	T	0.91	-2.28	0.49	2.8E-06	C	1.9E-01	-0.15	0.32	0.64	C	3.4E-01	3.3E-03	2.6E-03	0.20
rs16886290	5:20548631	T	0.91	-2.35	0.49	1.5E-06	G	1.8E-01	-0.15	0.32	0.64	G	3.4E-01	3.3E-03	2.6E-03	0.20
rs12514876	5:20552957	T	0.09	2.32	0.49	2.3E-06	T	1.8E-01	-0.15	0.32	0.63	T	3.4E-01	3.3E-03	2.6E-03	0.20
rs2002369	5:172895649	C	0.09	1.96	0.44	7.8E-06	NA	NA	NA	NA	NA	C	2.0E-03	8.5E-02	2.8E-02	2.73E-03
rs112331283	5:172897800	A	0.09	1.96	0.44	8.4E-06	NA	NA	NA	NA	NA	A	2.0E-03	8.5E-02	2.8E-02	2.73E-03
rs577755105	6:94266622	A	0.97	-4.11	0.93	9.8E-06	NA	NA	NA	NA	NA	G	2.6E-03	1.5E-02	2.5E-02	0.55
	6:123764858	c	0.63	1.25	0.28	8.5E-06	NA	NA	NA	NA	NA	G	2.3E-01	1.9E-03	3.0E-03	0.52
rs1736598	6:167682823	T	0.63	1.21	0.27	6.2E-06	C	1.7E-01	-0.11	0.32	0.74	C	2.1E-01	-7.7E-03	3.1E-03	0.01
rs1736599	6:167683244	A	0.64	1.24	0.27	3.6E-06	G	1.7E-01	-0.14	0.31	0.66	G	2.0E-01	-7.4E-03	3.1E-03	0.02
rs1736600	6:167683252	A	0.36	-1.24	0.27	3.6E-06	A	1.7E-01	-0.14	0.31	0.66	A	2.0E-01	-7.4E-03	3.1E-03	0.02
rs1736601	6:167683260	T	0.64	1.24	0.27	3.5E-06	C	1.7E-01	-0.14	0.31	0.66	C	2.0E-01	-7.4E-03	3.1E-03	0.02
rs1757120	6:167683392	T	0.64	1.22	0.27	4.2E-06	C	1.7E-01	-0.14	0.31	0.66	C	2.1E-01	-7.7E-03	3.1E-03	0.01
rs74939144	7:4020191	A	0.94	2.47	0.55	6.5E-06	NA	NA	NA	NA	NA	G	1.5E-03	-8.6E-03	3.3E-02	0.79
rs7458095	7:48176687	T	0.26	-1.33	0.29	5.0E-06	T	2.7E-01	-0.55	0.28	0.05	T	1.9E-01	1.3E-03	3.2E-03	0.68
rs11769253	7:48183283	T	0.2	-1.35	0.2	3.2E-06	T	2.7E-	-0.55	0.2	0.05	T	1.9E-	1.3E-	3.2E-	0.68

			5		9			01		8			01	03	03	
rs13437873	7:48189850	A	0.74	1.36	0.29	2.8E-06	G	2.7E-01	-0.50	0.28	0.07	G	1.9E-01	1.4E-03	3.2E-03	0.65
rs7458844	7:48195351	A	0.25	-1.36	0.29	3.1E-06	A	2.7E-01	-0.49	0.28	0.08	A	1.9E-01	1.2E-03	3.2E-03	0.70
rs139050038	7:48231980	A	0.74	1.32	0.29	6.2E-06	G	2.4E-01	-0.39	0.29	0.17	G	1.8E-01	1.6E-03	3.2E-03	0.61
rs112786750	7:136952150	A	0.03	4.00	0.89	6.6E-06	A	9.6E-02	0.06	0.42	0.88	A	3.9E-02	-6.3E-03	6.6E-03	0.34
rs77201625	7:136952328	A	0.03	3.63	0.78	2.8E-06	A	1.1E-01	0.32	0.41	0.43	A	6.3E-02	-1.3E-03	5.3E-03	0.81
rs78086971	7:136952882	C	0.04	3.58	0.75	1.6E-06	C	1.3E-01	-0.02	0.38	0.97	C	7.4E-02	2.1E-03	4.9E-03	0.67
rs141290008	8:8254059	A	0.04	-2.98	0.67	7.4E-06	NA	NA	NA	NA	NA	A	2.0E-03	3.0E-02	2.8E-02	0.29
rs7836839	8:8256178	c	0.96	2.91	0.64	5.1E-06	NA	NA	NA	NA	NA	G	2.0E-03	3.0E-02	2.8E-02	0.29
	8:19114322	T	0.90	-2.25	0.47	1.7E-06	NA	NA	NA	NA	NA	C	2.7E-01	-8.9E-04	3.0E-03	0.77
rs3935851	8:31133902	T	0.10	2.41	0.52	3.1E-06	T	2.2E-02	-0.31	0.85	0.72	T	2.4E-02	-2.2E-03	8.3E-03	0.79
rs931476	8:94396331	C	0.57	1.24	0.26	1.8E-06	G	4.0E-01	0.67	0.26	0.01	C	4.6E-01	-2.9E-03	2.6E-03	0.26
rs11780241	8:94400744	A	0.43	-1.23	0.26	1.8E-06	A	4.0E-01	0.68	0.26	0.01	G	4.6E-01	-3.2E-03	2.6E-03	0.21
rs2217516	8:94401023	A	0.57	1.24	0.26	1.6E-06	G	4.0E-01	0.68	0.26	0.01	A	4.6E-01	-3.2E-03	2.6E-03	0.21
rs2217515	8:94404371	A	0.43	-1.20	0.25	2.4E-06	A	4.0E-01	0.68	0.26	0.01	G	4.6E-01	-3.2E-03	2.6E-03	0.21
rs116328566	9:82465310	A	0.97	-3.51	0.74	1.8E-06	NA	NA	NA	NA	NA	G	4.1E-03	2.2E-02	2.0E-02	0.27
rs115548421	10:49913988	A	0.98	-4.22	0.91	3.3E-06	NA	NA	NA	NA	NA	T	5.1E-04	1.6E-02	5.7E-02	0.78
rs140531514	10:49920120	C	0.98	-4.10	0.88	2.8E-06	NA	NA	NA	NA	NA	G	5.1E-04	1.6E-02	5.7E-02	0.78
rs115354981	10:49922387	A	0.02	4.06	0.87	3.3E-06	NA	NA	NA	NA	NA	A	5.1E-04	1.6E-02	5.7E-02	0.78
	11:119954961	T	0.03	4.71	0.90	1.6E-07	NA	NA	NA	NA	NA	T	1.2E-02	-9.5E-04	1.2E-02	0.94
rs117420503	11:119975137	T	0.03	4.12	0.85	1.1E-06	T	1.3E-02	0.17	1.08	0.88	T	1.2E-02	-9.5E-04	1.2E-02	0.94
rs141363474	12:1281678	A	0.98	-4.07	0.92	9.8E-06	NA	NA	NA	NA	NA	G	1.5E-03	-3.7E-02	3.3E-02	0.25
rs145890129	12:1293336	C	0.02	4.28	0.93	4.5E-06	NA	NA	NA	NA	NA	C	1.5E-03	-3.7E-02	3.3E-02	0.25
rs147719909	12:1293805	T	0.98	-4.38	0.92	2.1E-06	NA	NA	NA	NA	NA	C	1.5E-03	-3.7E-02	3.3E-02	0.25

rs191656388	12:60543891	T	0.98	-4.27	0.91	3.0E-06	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs74422953	12:114762770	A	0.02	4.18	0.93	6.8E-06	NA	NA	NA	NA	NA	A	1.0E-03	1.7E-02	4.0E-02	0.68
rs802144	12:116293395	T	0.45	1.16	0.26	5.4E-06	T	3.2E-01	0.12	0.27	0.68	T	2.5E-01	6.0E-03	2.9E-03	0.04
rs7336381	13:114963436	A	0.77	-1.42	0.31	3.4E-06	T	2.6E-01	-0.25	0.29	0.38	T	2.3E-01	-3.1E-03	3.1E-03	0.32
rs146129483	15:53344844	C	0.11	1.88	0.41	4.5E-06	C	2.6E-03	-0.04	2.40	0.99	C	6.1E-03	-8.5E-03	1.6E-02	0.61
rs144212455	15:53363818	C	0.94	-2.59	0.54	1.9E-06	G	1.8E-03	0.35	2.95	0.91	G	5.1E-04	-6.8E-02	5.6E-02	0.23
rs80202087	15:78653983	A	0.10	-2.12	0.46	4.7E-06	A	1.9E-01	-0.21	0.32	0.51	A	1.7E-01	1.2E-03	3.4E-03	0.73
rs7500396	16:6903127	T	0.78	-1.36	0.31	9.5E-06	T	4.3E-01	-0.24	0.25	0.33	T	3.7E-01	-3.3E-03	2.6E-03	0.21
rs1492373	16:6946932	A	0.23	1.38	0.31	6.2E-06	G	4.7E-01	-0.13	0.25	0.60	G	3.8E-01	-8.8E-04	2.6E-03	0.74
rs1974859	16:26743655	T	0.42	1.16	0.26	8.7E-06	T	3.4E-01	-0.47	0.26	0.07	C	4.7E-01	-3.8E-03	2.5E-03	0.14
rs1974858	16:26743681	A	0.42	-1.23	0.26	2.8E-06	A	3.0E-01	0.31	0.27	0.25	A	2.8E-01	-3.6E-03	2.8E-03	0.20
rs7199153	16:75016702	A	0.04	3.13	0.70	7.1E-06	NA	NA	NA	NA	NA	A	1.0E-03	-6.5E-02	4.0E-02	0.11
rs7201798	16:75019271	C	0.04	3.11	0.70	7.8E-06	NA	NA	NA	NA	NA	C	1.0E-03	-6.5E-02	4.0E-02	0.11
rs76568462	17:63334681	T	0.09	-2.02	0.45	7.8E-06	T	1.7E-02	-0.68	0.92	0.46	T	2.8E-02	-3.0E-03	7.9E-03	0.70
rs7240881	18:11137737	A	0.95	2.60	0.58	7.8E-06	G	2.0E-01	0.11	0.30	0.72	G	1.9E-01	4.6E-05	3.4E-03	0.99
	18:63446314	T	0.51	1.42	0.30	2.4E-06	NA	NA	NA	NA	NA	T	2.4E-01	-1.8E-03	3.1E-03	0.56
rs114205345	18:67635347	T	0.03	4.05	0.81	5.8E-07	NA	NA	NA	NA	NA	T	5.1E-04	1.1E-02	5.6E-02	0.84
rs139816609	18:67651944	T	0.03	3.79	0.81	2.7E-06	T	8.8E-04	-1.53	4.14	0.71	T	5.1E-04	1.1E-02	5.6E-02	0.84
rs819166	20:32839116	A	0.13	1.69	0.38	9.4E-06	A	9.8E-02	-0.33	0.41	0.43	A	6.0E-02	4.3E-03	5.5E-03	0.44
rs6088448	20:32841556	T	0.13	1.66	0.38	9.5E-06	T	9.8E-02	-0.33	0.41	0.43	T	6.0E-02	4.3E-03	5.5E-03	0.44
rs113507899	20:47269282	A	0.04	3.24	0.65	6.9E-07	A	1.8E-03	-1.65	2.95	0.58	A	1.5E-03	4.4E-03	3.3E-02	0.89
rs7269602	20:47272778	A	0.04	3.20	0.65	9.3E-07	NA	NA	NA	NA	NA	A	1.5E-03	4.4E-03	3.3E-02	0.89
rs62621889	20:47274733	T	0.97	-3.70	0.71	1.6E-07	NA	NA	NA	NA	NA	C	1.5E-03	4.4E-03	3.3E-02	0.89
	20:47281780	T	0.9	-3.66	0.7	8.7E-07	NA	NA	NA	NA	NA	C	1.5E-	4.4E-	3.3E-	0.89

				6		4								03	03	02	
	rs73911623	20:47286616	T	0.03	3.51	0.70	5.4E-07	NA	NA	NA	NA	NA	T	1.5E-03	4.4E-03	3.3E-02	0.89
	rs73911633	20:47302075	A	0.96	-3.44	0.68	4.7E-07	NA	NA	NA	NA	NA	G	2.0E-03	-1.1E-02	2.8E-02	0.70
	rs60933803	20:47317671	A	0.03	3.28	0.73	8.0E-06	NA	NA	NA	NA	NA	A	5.1E-04	-5.6E-02	5.6E-02	0.32
	rs73911643	20:47328586	A	0.97	-3.28	0.73	7.1E-06	NA	NA	NA	NA	NA	C	5.1E-04	-5.6E-02	5.6E-02	0.32
	rs141655482	20:47329519	A	0.03	3.27	0.73	7.4E-06	NA	NA	NA	NA	NA	A	5.1E-04	-5.6E-02	5.6E-02	0.32
	rs74690665	20:47330344	T	0.97	-3.28	0.73	7.3E-06	NA	NA	NA	NA	NA	C	5.1E-04	-5.6E-02	5.6E-02	0.32
	rs73911646	20:47332997	A	0.03	3.27	0.73	7.4E-06	NA	NA	NA	NA	NA	A	5.1E-04	-5.6E-02	5.6E-02	0.32
	rs73150065	20:47334279	T	0.08	2.27	0.47	1.6E-06	T	1.7E-01	-0.17	0.33	0.61	T	2.6E-01	-1.0E-03	3.0E-03	0.72
	rs61291953	20:47334520	C	0.08	2.27	0.47	1.6E-06	C	1.7E-01	-0.17	0.33	0.61	C	2.6E-01	-1.0E-03	3.0E-03	0.72
	rs73911651	20:47336958	A	0.03	3.24	0.73	9.0E-06	NA	NA	NA	NA	NA	A	5.1E-04	-5.6E-02	5.6E-02	0.32
	rs12480741	20:47337525	C	0.09	2.02	0.45	6.9E-06	C	1.7E-01	-0.17	0.33	0.61	C	2.6E-01	-1.0E-03	3.0E-03	0.72
	rs73911660	20:47344867	A	0.03	3.26	0.73	8.2E-06	NA	NA	NA	NA	NA	A	5.1E-04	-5.6E-02	5.6E-02	0.32
	rs73911663	20:47348961	T	0.03	3.27	0.73	7.9E-06	NA	NA	NA	NA	NA	T	5.1E-04	-5.6E-02	5.6E-02	0.32
	rs180690421	22:47555306	A	0.96	-3.04	0.69	9.9E-06	NA	NA	NA	NA	NA	C	6.1E-03	1.1E-02	1.6E-02	0.51
		22:47561184	T	0.97	-5.26	0.95	3.3E-08	NA	NA	NA	NA	NA	G	3.6E-03	1.6E-02	2.1E-02	0.47
		22:47561191	A	0.97	-5.19	0.93	2.8E-08	NA	NA	NA	NA	NA	G	3.6E-03	1.6E-02	2.1E-02	0.47
	rs148151878	22:47561214	A	0.95	-2.73	0.60	6.4E-06	NA	NA	NA	NA	NA	G	6.1E-03	1.1E-02	1.6E-02	0.51
			Combined Meta-analysis					Validation in CAMP study (White sample)					Validation in Costa Rica Study (Hispanic sample)				
Phenotype	**SNP**	**Chr:Position**	**Allele**	**AF**	**Effect**	**SE**	**p-value**	**Allele**	**AF**	**Effect**	**SE**	**p-value**	**Allele**	**AF**	**Effect**	**SE**	**p-value**
FEV1	rs1953833	1:239941671	A	0.71	-0.54	0.12	3.6E-06	G	2.6E-01	0.05	0.52	0.92	G	2.8E-01	-7.5E-03	3.7E-03	0.04
	rs140005306	2:143707656	A	0.95	1.20	0.26	3.0E-06	G	5.8E-02	-0.18	0.97	0.85	G	6.9E-02	-1.2E-03	6.6E-03	0.85
	rs6771660	3:6249803	T	0.40	-1.26	0.26	1.3E-06	NA	NA	NA	NA	NA	T	3.8E-01	-3.3E-03	3.3E-03	0.32
	rs6769069	3:6249806	A	0.40	-1.26	0.26	1.3E-06	NA	NA	NA	NA	NA	A	3.8E-01	-3.3E-03	3.3E-03	0.32

	rs6780151	3:6249820	A	0.60	1.26	0.26	1.2E-06	NA	NA	NA	NA	NA	G	3.8E-01	-3.3E-03	3.3E-03	0.32
	rs9868510	3:105700120	A	0.51	-0.52	0.11	2.1E-06	C	4.4E-01	0.55	0.47	0.24	C	4.9E-01	6.9E-03	3.4E-03	0.05
	rs9814261	3:105700717	T	0.49	0.51	0.11	3.2E-06	T	4.4E-01	0.55	0.47	0.24	T	4.9E-01	6.9E-03	3.4E-03	0.05
	rs9869772	3:105700732	c	0.51	-0.51	0.11	3.2E-06	G	4.4E-01	0.55	0.47	0.24	G	4.9E-01	6.9E-03	3.4E-03	0.05
	rs9387998	6:122074243	A	0.90	0.88	0.19	3.0E-06	T	8.9E-02	-0.40	0.81	0.62	T	6.2E-02	3.7E-03	6.9E-03	0.59
	rs9385215	6:122074667	A	0.10	-0.88	0.19	2.7E-06	A	8.9E-02	-0.40	0.81	0.62	A	6.3E-02	2.6E-03	6.9E-03	0.70
	rs13262811	8:142425325	A	0.86	0.76	0.16	2.2E-06	G	1.5E-01	0.08	0.64	0.90	G	2.0E-01	-9.7E-03	4.1E-03	0.02
	rs7079679	10:102055546	A	0.53	0.50	0.11	3.0E-06	C	4.9E-01	-0.04	0.47	0.94	C	3.4E-01	4.2E-03	3.5E-03	0.24
	rs186201422	10:133458567	T	0.06	-2.85	0.62	3.7E-06	NA	NA	NA	NA	NA	T	2.7E-02	-1.4E-03	1.0E-02	0.90
	rs144465006	11:18273453	A	0.08	-2.35	0.51	3.5E-06	NA	NA	NA	NA	NA	A	7.2E-03	-2.9E-02	2.0E-02	0.14
	rs11055259	12:13325209	A	0.94	-1.12	0.23	1.9E-06	G	5.1E-02	-1.12	1.09	0.31	G	7.4E-02	-3.2E-03	6.2E-03	0.60
	rs11055261	12:13325396	c	0.06	1.11	0.23	2.1E-06	C	5.1E-02	-1.12	1.09	0.31	C	7.4E-02	-3.2E-03	6.2E-03	0.60
	rs11055263	12:13327373	A	0.95	-1.13	0.24	2.7E-06	G	5.0E-02	-1.06	1.10	0.34	G	7.3E-02	-2.5E-03	6.2E-03	0.68
	rs11055266	12:13329382	T	0.06	1.13	0.23	1.6E-06	T	5.1E-02	-1.11	1.09	0.31	T	7.4E-02	-3.4E-03	6.2E-03	0.58
	rs74063255	12:13329613	A	0.06	1.07	0.23	2.5E-06	A	5.1E-02	-1.11	1.09	0.31	A	7.9E-02	-2.9E-03	6.0E-03	0.63
	rs11055267	12:13329855	A	0.93	-1.14	0.23	1.1E-06	G	5.0E-02	-1.06	1.10	0.34	G	7.3E-02	-3.0E-03	6.3E-03	0.64
	rs11055268	12:13330247	T	0.95	-1.13	0.24	1.9E-06	C	5.5E-02	-0.97	1.05	0.36	C	7.4E-02	-3.2E-03	6.3E-03	0.61
	rs11055270	12:13331931	T	0.05	1.18	0.25	1.5E-06	T	5.4E-02	-0.35	1.07	0.75	T	7.5E-02	-9.8E-04	6.2E-03	0.87
	rs4782614	16:84396105	A	0.32	0.64	0.12	7.5E-08	A	2.8E-01	0.26	0.51	0.61	A	3.5E-01	-3.8E-04	3.5E-03	0.91
	rs76890972	16:84399755	A	0.08	1.02	0.21	1.6E-06	A	7.8E-02	-0.63	0.88	0.47	A	6.2E-02	5.9E-03	7.0E-03	0.39
	rs10426116	19:44591553	T	0.06	2.56	0.52	1.1E-06	NA	NA	NA	NA	NA	T	1.0E-03	6.0E-02	5.2E-02	0.25
FVC	rs113168856	2:110275743	A	0.11	1.87	0.41	4.3E-06	A	8.8E-04	2.87	4.14	0.49	A	1.2E-02	-1.0E-02	1.2E-02	0.37
	rs112287970	2:110277555	T	0.11	1.86	0.41	4.9E-06	T	8.8E-04	2.87	4.14	0.49	T	1.2E-02	-1.0E-02	1.2E-02	0.37
	rs11316358	2:110294414	T	0.1	1.99	0.4	1.8E-06	T	8.8E-	2.87	4.1	0.49	T	1.5E-	-2.1E-	1.0E-	0.84

5			0		2			04		4			02	03	02	
rs113163838	2:110312411	A	0.06	2.58	0.52	8.9E-07	A	8.8E-04	2.87	4.14	0.49	A	7.7E-03	-1.1E-02	1.5E-02	0.44
rs28440810	2:110322704	c	0.06	2.57	0.52	9.3E-07	C	8.8E-04	2.87	4.14	0.49	C	7.2E-03	-9.8E-03	1.5E-02	0.52
rs113307559	2:110323889	T	0.06	2.57	0.52	9.3E-07	T	8.8E-04	2.87	4.14	0.49	T	7.2E-03	-9.8E-03	1.5E-02	0.52
rs111452745	2:110331092	T	0.09	2.17	0.43	5.0E-07	T	8.8E-04	2.87	4.14	0.49	T	1.2E-02	-5.3E-03	1.2E-02	0.65
rs112462060	2:110346916	T	0.06	2.59	0.53	1.0E-06	T	8.8E-04	2.87	4.14	0.49	T	7.2E-03	-9.8E-03	1.5E-02	0.52
rs111566351	2:110360671	A	0.91	-2.23	0.44	3.7E-07	T	8.8E-04	2.87	4.14	0.49	T	1.1E-02	-9.3E-03	1.2E-02	0.44
rs112450144	2:110360823	A	0.09	2.20	0.44	5.3E-07	A	3.5E-03	1.46	2.08	0.48	A	1.2E-02	-9.0E-03	1.2E-02	0.44
rs187889188	2:110361687	T	0.09	2.23	0.44	3.6E-07	T	8.8E-04	2.87	4.14	0.49	T	1.1E-02	-9.3E-03	1.2E-02	0.44
rs113520112	2:110362336	c	0.09	2.24	0.44	3.6E-07	C	8.8E-04	2.87	4.14	0.49	C	1.1E-02	-9.3E-03	1.2E-02	0.44
rs74868086	2:110373165	A	0.06	2.70	0.54	5.1E-07	A	8.8E-04	2.87	4.14	0.49	A	6.1E-03	-9.3E-03	1.6E-02	0.57
rs76992194	2:110373468	A	0.94	-2.63	0.52	3.9E-07	G	8.8E-04	2.87	4.14	0.49	G	6.1E-03	-9.3E-03	1.6E-02	0.57
rs113001438	2:110376483	c	0.94	-2.72	0.54	4.8E-07	G	8.8E-04	2.87	4.14	0.49	G	6.1E-03	-9.3E-03	1.6E-02	0.57
rs111634292	2:110381056	A	0.06	2.74	0.54	4.6E-07	A	8.8E-04	2.87	4.14	0.49	A	6.1E-03	-9.3E-03	1.6E-02	0.57
rs112520760	2:110383702	A	0.06	2.76	0.55	4.4E-07	A	8.8E-04	2.87	4.14	0.49	A	6.1E-03	-9.3E-03	1.6E-02	0.57
rs111666992	2:110398852	A	0.94	-2.87	0.57	4.7E-07	T	8.8E-04	2.87	4.14	0.49	T	6.1E-03	-9.3E-03	1.6E-02	0.57
rs59724818	2:110405235	T	0.93	-2.59	0.56	4.2E-06	G	8.8E-04	2.87	4.14	0.49	G	5.6E-03	-1.2E-02	1.7E-02	0.47
rs114776525	2:110409387	A	0.06	2.84	0.59	1.7E-06	A	8.8E-04	2.87	4.14	0.49	A	2.6E-03	-1.6E-02	2.5E-02	0.54
rs28636565	2:110410070	A	0.94	-2.84	0.59	1.6E-06	G	8.8E-04	2.87	4.14	0.49	G	2.6E-03	-1.6E-02	2.5E-02	0.54
rs28626622	2:110413792	c	0.06	2.86	0.59	1.3E-06	C	8.8E-04	2.87	4.14	0.49	C	2.6E-03	-1.6E-02	2.5E-02	0.54
rs28549324	2:110414161	T	0.06	2.84	0.59	1.7E-06	T	8.8E-04	2.87	4.14	0.49	T	2.6E-03	-1.6E-02	2.5E-02	0.54
rs7600969	2:110434663	T	0.06	2.02	0.43	2.2E-06	T	1.1E-02	0.28	1.16	0.81	T	6.3E-02	1.6E-03	5.3E-03	0.77
rs73803631	4:24159527	A	0.91	2.08	0.45	4.5E-06	C	8.8E-04	-2.72	4.14	0.51	C	5.1E-03	-6.9E-03	1.8E-02	0.70
rs55699229	8:19114322	T	0.90	-2.25	0.47	1.7E-06	NA	NA	NA	NA	NA	C	2.7E-01	-8.9E-04	3.0E-03	0.77

rs75638212	10:22950466	T	0.86	-0.74	0.15	1.0E-06	G	1.3E-01	-0.94	0.38	0.01	G	8.5E-02	-2.5E-03	4.5E-03	0.57
rs146129483	15:53344844	c	0.11	1.88	0.41	4.5E-06	C	2.6E-03	-0.04	2.40	0.99	C	6.1E-03	-8.5E-03	1.6E-02	0.61
rs144212455	15:53363818	c	0.94	-2.59	0.54	1.9E-06	G	1.8E-03	0.35	2.95	0.91	G	5.1E-04	-6.8E-02	5.6E-02	0.23
rs4782614	16:84396105	A	0.32	0.57	0.12	2.5E-06	A	2.8E-01	0.07	0.27	0.79	A	3.5E-01	9.2E-04	2.7E-03	0.73
rs71355331	18:45645902	T	0.94	1.12	0.24	3.6E-06	C	6.6E-02	0.17	0.50	0.74	C	2.8E-02	-6.9E-03	7.8E-03	0.38
rs199964754	18:63446314	T	0.51	1.42	0.30	2.4E-06	NA	NA	NA	NA	NA	T	2.4E-01	-1.8E-03	3.1E-03	0.56

Table S4. Allele frequency, effect size (beta or odds ratio (OR), as reported by each individual study), and p-value of SNPs that reached genome-wide significance ($p<5\times10^{-8}$) in association studies of bronchodilator response (percent change or absolute change in FEV1), chronic obstructive pulmonary disease (COPD), and asthma, with the results for same SNPs in this GWAS meta-analysis of bronchodilator response (percent change in FEV1).

			Literature GWAS of BDR, COPD, or asthma				GWAS stratified meta-analysis of BDR				Combined meta-anlaysis GWAS			
Paper	**Phenotype**	**SNP**	**Allele**	**Allele Freq**	**Beta**	**P-value**	**Allele**	**Allele Freq**	**Beta**	**P-value**	**Allele**	**Allele Freq**	**Beta**	**P-value**
Israel et al.(1)	BDR percent change FEV1	rs350729	T	>5%	-5.63	2.21×10^{-10}	T	0.32	-0.01	0.95	T	0.32	0.00	1.00
		rs1319797	G	>5%	-5	3.95×10^{-8}	G	0.39	-0.05	0.78	A	0.61	0.01	0.93
Drake et al.(2)	BDR percent change FEV1	rs8191725	G	0.82%	10.2	3.3×10^{-9}	G	0.03	-0.17	0.73	A	0.97	0.17	0.73
		rs77977790	C	2.80%	9.5	4.6×10^{-10}	C	0.05	-0.13	0.74	T	0.95	0.14	0.74
		rs77149876	C	0.18%	32.5	1.4×10^{-8}	C	0.01	-1.11	0.37	T	0.99	1.11	0.37

		rs74973995	G	0.18%	32.6	1.3×10^{-8}	G	0.02	-0.09	0.92	A	0.98	0.09	0.92
		rs115501901	T	0.0018	31.5	4.2×10^{-8}	T	N/A	N/A	N/A	T	0.02	-4.10	0.26
Spear et al.(3)	BDR percent change FEV1	rs7070958	A	N/A	-1.24	4.09×10^{-8}	A	0.71	0.1	0.6	A	0.69	0.13	0.48
		rs7081864	A	N/A	1.23	4.94×10^{-8}	A	0.28	-0.1	0.61	A	0.31	-0.12	0.49
		rs7903366	T	N/A	1.23	3.94×10^{-8}	T	0.28	-0.09	0.63	T	0.31	-0.11	0.53
Hardin et al.(4)	BDR absolute change FEV1	rs17575208	A	0.99	0.11	8.92×10^{-9}	A	0.97	0.25	0.75	A	0.99	0.25	0.75
		rs10056066	A	0.07	7.12	4.86×10^{-8}	N/A	N/A	N/A	N/A	A	0.07	0.69	0.62
		rs115067260	A	0.97	0.17	5.05×10^{-9}	N/A	N/A	N/A	N/A	A	0.97	-0.05	0.98
		rs140948272	C	0.99	0.33	5.24×10^{-9}	N/A	N/A	N/A	N/A	T	0.02	-3.13	0.32
Mak et al.(5)	BDR percent change FEV1	rs17834628	A	0.32/0.47/0.17*	1.67	1.18×10^{-8}	A	0.36	-0.13	0.47	A	0.35	-0.11	0.53
		rs35661809	G	0.34/0.43/0.24*	1.59	3.33×10^{-8}	G	0.36	0.08	0.63	A	0.64	0.05	0.75
Zhao et al.(6)	COPD	rs11331126	A	0.35	0.34	6.0E-09	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		rs11687134	T	0.72	-0.34	2.7E-08	t	0.72	-0.31	0.09	t	0.72	-0.31	0.09
		rs12914385	T	0.34	0.28	8.8E-12	t	0.42	0.03	0.84	t	0.41	0.67	0.41
		rs12914385	T	0.32	0.20	1.8E-10	t	0.42	0.03	0.84	t	0.41	0.67	0.41
		rs12914385	T	0.34	0.33	1.6E-09	t	0.42	0.03	0.84	t	0.41	0.67	0.41
		rs1512281	G	0.31	-0.34	2.6E-09	a	0.60	-0.11	0.51	a	0.61	-0.11	0.54
		rs17486278	C	0.33	0.31	4.7E-10	a	0.62	0.08	0.63	a	0.63	0.11	0.53
		rs4416442	C	0.45	0.17	2.4E-08	t	0.60	0.16	0.37	t	0.59	0.15	0.38
		rs4416442	C	0.45	0.22	1.2E-08	t	0.60	0.16	0.37	t	0.59	0.15	0.38
		rs72740913	T	0.01	1.08	3.3E-08	t	0.01	-0.56	0.51	t	0.01	-0.56	0.51
		rs7682317	T	0.40	0.27	3.7E-08	t	0.40	-0.16	0.37	t	0.41	-0.14	0.41
		rs7682317	T	0.44	0.30	1.1E-08	t	0.40	-0.16	0.37	t	0.41	-0.14	0.41
		rs8040868	C	0.42	0.27	2.4E-08	t	0.57	-0.02	0.91	t	0.57	-0.63	0.41
		rs8040868	C	0.41	0.21	9.5E-09	t	0.57	-0.02	0.91	t	0.57	-0.63	0.41

		rs8040868	C	0.42	0.34	8.3E-09	t	0.57	-0.02	0.91	t	0.57	-0.63	0.41
Sakornsakolpat et al.(7)	COPD	rs10037493	T	0.45	-0.12	2.6E-33	t	0.43	-0.05	0.79	t	0.43	-0.04	0.80
		rs10114763	A	0.58	-0.07	8.7E-13	a	0.57	-0.27	0.11	a	0.57	0.12	0.84
		rs10152300	A	0.77	-0.08	4.2E-12	a	0.77	0.39	0.05	a	0.77	-0.86	0.58
		rs10760580	A	0.29	-0.07	1.2E-10	a	0.28	0.00	0.99	a	0.28	0.45	0.56
		rs10866659	A	0.65	-0.08	1.2E-16	a	0.64	-0.11	0.51	a	0.63	-0.32	0.41
		rs10929386	T	0.51	-0.06	9.1E-09	t	0.52	-0.10	0.57	t	0.52	-0.13	0.42
		rs11049386	A	0.29	-0.06	2.7E-08	a	0.28	-0.15	0.43	a	0.28	0.49	0.63
		rs11118406	A	0.72	-0.07	4.1E-11	a	0.72	0.03	0.85	a	0.70	0.06	0.73
		rs11579382	C	0.42	0.06	6.5E-09	c	0.42	-0.16	0.35	c	0.42	-0.19	0.26
		rs11655567	T	0.51	-0.06	1.9E-09	t	0.52	0.10	0.54	t	0.53	0.08	0.62
		rs117261012	A	0.84	-0.08	6.9E-10	a	0.84	-0.25	0.28	a	0.84	-0.25	0.28
		rs12373142	C	0.78	-0.07	9.9E-10	c	0.78	-0.06	0.76	c	0.78	-0.07	0.71
		rs12466981	T	0.27	-0.06	4.9E-08	t	0.27	-0.04	0.85	t	0.26	-0.02	0.91
		rs12519165	A	0.38	0.07	1.1E-09	a	0.38	-0.25	0.17	a	0.39	0.21	0.75
		rs13073544	C	0.28	0.06	2.0E-08	c	0.29	0.03	0.86	c	0.29	0.01	0.97
		rs13140176	A	0.61	0.17	4.1E-59	a	0.61	-0.06	0.73	a	0.62	-0.04	0.82
		rs13198656	T	0.56	0.06	1.2E-09	t	0.57	0.01	0.98	t	0.55	0.00	1.00
		rs1334576	A	0.42	0.06	1.2E-08	a	0.42	-0.25	0.14	a	0.41	-0.25	0.12
		rs1441358	T	0.66	-0.12	7.4E-33	t	0.66	0.06	0.73	t	0.65	-0.56	0.46
		rs1529672	A	0.17	-0.09	2.5E-11	a	0.17	0.03	0.88	a	0.17	-0.44	0.52
		rs153916	T	0.55	0.06	6.3E-10	t	0.54	0.14	0.40	t	0.54	0.13	0.43
		rs1551943	A	0.23	0.07	5.8E-10	a	0.24	0.14	0.47	a	0.24	0.16	0.40
		rs156394	T	0.53	0.07	3.8E-12	N/A	N/A	N/A	N/A	t	0.54	-0.13	0.42
		rs1570221	A	0.35	0.06	2.2E-08	a	0.35	-0.02	0.92	a	0.35	-0.02	0.92
		rs16825267	C	0.92	0.18	1.8E-20	c	0.93	-0.05	0.88	c	0.93	0.01	0.96

rs17759204	A	0.73	-0.07	8.8E-11	a	0.72	-0.10	0.57	a	0.72	-0.09	0.62
rs2040732	T	0.42	-0.06	6.9E-09	t	0.42	-0.12	0.46	t	0.42	-0.15	0.37
rs2047409	A	0.63	0.08	1.9E-16	a	0.62	0.19	0.28	a	0.61	0.19	0.25
rs2070600	T	0.06	-0.19	1.1E-17	t	0.04	0.22	0.60	t	0.04	0.22	0.60
rs2076295	T	0.54	0.06	1.2E-08	t	0.55	0.10	0.54	t	0.55	0.07	0.68
rs2096468	A	0.45	0.05	4.0E-08	a	0.46	-0.03	0.84	a	0.46	-0.36	0.47
rs2119568	T	0.82	-0.19	4.0E-11	t	0.82	-0.23	0.28	t	0.82	-0.41	0.38
rs2284174	T	0.78	-0.12	2.1E-21	t	0.80	-0.07	0.74	t	0.78	-0.12	0.55
rs2442776	A	0.85	-0.09	2.0E-10	a	0.86	-0.20	0.42	a	0.85	-0.15	0.52
rs2571445	A	0.39	0.07	3.4E-12	a	0.40	-0.22	0.19	a	0.39	0.76	0.50
rs2579762	A	0.53	-0.06	2.6E-10	a	0.52	-0.19	0.24	a	0.53	0.74	0.50
rs2806356	T	0.82	-0.10	2.9E-15	t	0.81	0.36	0.09	t	0.81	0.38	0.07
rs2897075	T	0.37	-0.06	7.3E-10	t	0.37	0.00	0.98	t	0.37	0.00	0.98
rs2955083	A	0.88	0.12	3.5E-15	a	0.88	-0.12	0.63	a	0.88	-0.16	0.51
rs3009947	T	0.50	-0.06	4.0E-09	t	0.48	-0.07	0.69	t	0.49	-0.15	0.53
rs34651	T	0.92	-0.10	3.0E-08	t	0.92	-0.38	0.22	t	0.92	-0.41	0.19
rs34712979	A	0.25	0.17	3.0E-46	a	0.26	0.11	0.61	a	0.26	0.12	0.56
rs34727469	T	0.14	0.08	1.1E-08	t	0.14	-0.20	0.42	t	0.14	-0.17	0.48
rs35584079	A	0.14	0.08	9.0E-09	a	0.13	0.25	0.32	a	0.17	0.22	0.36
rs4093840	A	0.47	0.06	3.9E-10	a	0.47	0.08	0.62	a	0.47	-0.11	0.78
rs4143333	A	0.88	-0.10	7.6E-09	a	0.91	0.01	0.97	a	0.91	0.02	0.95
rs4585380	A	0.26	-0.07	3.4E-09	a	0.26	-0.35	0.07	a	0.26	-0.37	0.05
rs4660861	T	0.43	-0.05	4.4E-08	t	0.44	0.11	0.50	t	0.44	0.10	0.53
rs4757118	T	0.54	0.06	3.8E-09	t	0.56	0.00	0.99	t	0.55	-0.16	0.68
rs4888379	A	0.42	-0.09	5.9E-21	a	0.40	-0.17	0.31	a	0.42	-0.18	0.27
rs55676755	C	0.66	-0.11	2.8E-26	c	0.62	0.07	0.68	c	0.63	-0.47	0.53

rs56134392	T	0.65	-0.06	4.5E-08	t	0.66	0.18	0.31	t	0.64	0.41	0.32
rs62065216	A	0.42	0.06	8.1E-09	a	0.42	0.23	0.18	a	0.42	0.23	0.17
rs62191105	T	0.20	-0.09	2.6E-12	t	0.21	-0.06	0.78	t	0.20	-0.03	0.87
rs62259026	T	0.25	-0.06	2.4E-08	t	0.25	-0.18	0.35	t	0.25	-0.20	0.27
rs62375246	A	0.26	0.06	2.2E-08	a	0.27	0.25	0.19	a	0.27	0.26	0.16
rs629619	T	0.20	0.08	2.9E-10	t	0.19	-0.05	0.82	t	0.19	-0.40	0.48
rs646695	T	0.76	-0.07	4.6E-11	t	0.75	-0.27	0.16	t	0.76	-0.26	0.17
rs647097	T	0.73	-0.07	1.0E-11	t	0.71	-0.12	0.52	t	0.71	-0.04	0.85
rs674621	T	0.68	-0.06	7.6E-09	t	0.67	0.16	0.38	t	0.68	0.19	0.27
rs7068966	T	0.51	-0.10	6.2E-23	t	0.52	-0.33	0.05	t	0.50	-0.34	0.04
rs721917	A	0.58	-0.05	2.2E-08	a	0.57	-0.31	0.06	a	0.57	-0.05	0.92
rs72626215	A	0.27	-0.07	1.7E-09	a	0.27	0.02	0.90	a	0.26	0.63	0.46
rs72673419	T	0.05	0.13	4.0E-09	t	0.05	-0.77	0.05	t	0.05	-0.45	0.47
rs72673891	A	0.93	0.13	1.5E-09	a	0.93	0.23	0.51	a	0.93	0.21	0.54
rs72699855	C	0.19	-0.07	4.8E-09	c	0.18	0.17	0.45	c	0.18	0.16	0.46
rs72731149	C	0.09	-0.11	8.3E-09	c	0.07	0.57	0.09	c	0.09	0.59	0.06
rs72902175	T	0.13	0.08	1.6E-08	t	0.13	-0.02	0.93	t	0.13	0.55	0.63
rs7307510	T	0.19	-0.07	2.6E-09	t	0.19	-0.14	0.50	t	0.19	-0.13	0.52
rs73158393	C	0.74	0.07	7.7E-09	c	0.75	-0.03	0.88	c	0.76	0.22	0.73
rs7642001	A	0.37	0.08	1.1E-14	a	0.37	0.02	0.89	a	0.36	0.02	0.93
rs7650602	T	0.55	-0.05	4.9E-08	t	0.56	-0.01	0.95	t	0.54	-0.04	0.79
rs7671261	A	0.55	0.09	1.4E-18	a	0.54	0.15	0.37	a	0.55	0.12	0.47
rs76841360	A	0.23	0.07	5.0E-10	a	0.23	0.04	0.82	a	0.22	0.03	0.86
rs7866939	T	0.67	-0.06	1.8E-08	t	0.68	0.00	0.99	t	0.66	-0.03	0.88
rs7958945	A	0.64	-0.06	1.0E-09	a	0.64	-0.15	0.38	a	0.62	-0.15	0.39
rs798565	A	0.29	-0.07	3.9E-09	a	0.29	0.09	0.63	a	0.28	0.16	0.56
rs803923	A	0.53	0.05	2.7E-08	a	0.55	-0.09	0.58	a	0.54	-0.07	0.66

		rs8044657	A	0.10	-0.10	1.1E-08	a	0.09	0.04	0.90	a	0.12	0.01	0.96
		rs8080772	T	0.64	0.06	1.4E-08	t	0.65	-0.06	0.71	t	0.66	-0.07	0.70
		rs9273404	A	0.53	-0.08	2.0E-11	a	0.69	-0.09	0.82	a	0.70	-0.11	0.76
		rs9329170	C	0.86	0.09	3.6E-10	c	0.86	0.08	0.73	c	0.85	0.86	0.36
		rs9350191	T	0.85	0.11	5.1E-14	t	0.85	0.05	0.86	t	0.85	0.07	0.76
		rs9399401	T	0.72	0.15	1.6E-40	t	0.73	0.15	0.44	t	0.72	0.33	0.36
		rs9435731	A	0.51	0.06	6.6E-10	a	0.52	0.06	0.72	a	0.51	0.92	0.37
		rs9525927	A	0.81	-0.07	2.8E-09	a	0.81	-0.12	0.57	a	0.81	-0.12	0.55
		rs955277	T	0.61	0.07	1.9E-10	t	0.62	-0.13	0.47	t	0.61	-0.15	0.39
		rs9617650	C	0.21	-0.08	4.4E-10	c	0.21	0.14	0.51	c	0.21	0.16	0.45
		rs979453	A	0.66	-0.06	1.4E-08	a	0.66	-0.23	0.21	a	0.64	-0.24	0.18
Cho et al.(8)	COPD	rs7937	T	0.44	0.74	2.9×10^{-9}	T	0.57	0.04	0.8	t	0.56	0.07	0.66
Busch et al.(9)	COPD	rs28929474	T	0.01	1.84	2.0×10^{-8}	T	0.02	-1	0.08	t	0.02	-1.00	0.08
Cho et al.(10)	COPD	rs626750	G	0.83	1.36	5.3×10^{-9}	A	0.18	0.14	0.5	a	0.18	0.12	0.58
Demenais et al.(11)	Asthma	rs10455025	A	0.34	1.15	2.0×10^{-25}	a	0.64	-0.004	0.9821	c	0.65	-0.01	0.94
		rs11071558	A	0.14	0.89	1.9 × 10−10	a	0.86	-0.0061	0.9799	g	0.84	-0.06	0.79
		rs1233578	A	0.13	1.11	5.3×10^{-9}	a	0.86	0.1968	0.4095	g	0.83	0.24	0.29
		rs12543811	G	0.66	0.93	3.4×10^{-8}	a	0.64	0.0581	0.7369	g	0.63	0.02	0.89
		rs1420101	C	0.37	1.12	9.1×10^{-20}	t	0.38	-0.0281	0.8691	c	0.37	-0.34	0.50
		rs167769	C	0.4	1.08	1.6×10^{-7}	t	0.38	0.0298	0.8656	c	0.36	0.04	0.83
		rs17637472	G	0.39	1.08	3.3×10^{-9}	a	0.41	-0.2163	0.205	g	0.40	-0.21	0.21
		rs17806299	G	0.2	0.9	2.1×10^{-10}	a	0.21	0.2165	0.2878	g	0.21	0.24	0.24
		rs2033784	A	0.3	1.11	2.5×10^{-14}	a	0.3	0.1373	0.4446	g	0.69	-0.23	0.67
		rs20541	A	0.79	0.89	1.4×10^{-14}	a	0.8	0.0009	0.9965	g	0.19	0.12	0.72
		rs2325291	G	0.33	0.91	8.6×10^{-13}	a	0.34	-0.03	0.8638	g	0.33	-0.05	0.76

rs2589561	A	0.82	0.9	1.4×10^{-8}	a	0.81	-0.0768	0.7239	g	0.18	-0.07	0.73
rs2855812	G	0.23	1.1	1.7×10^{-8}	t	0.23	-0.2247	0.2475	g	0.24	-0.34	0.26
rs2952156	A	0.7	0.86	7.6×10^{-29}	a	0.69	-0.0239	0.8945	g	0.32	0.19	0.63
rs7705042	C	0.63	1.08	1.6×10^{-6}	a	0.63	0.1778	0.2982	c	0.64	0.18	0.28
rs7927894	C	0.37	1.1	3.5×10^{-11}	t	0.39	-0.0206	0.905	c	0.38	-0.04	0.81
rs9272346	G	0.56	1.16	4.8×10^{-28}	a	0.58	0.2212	0.2039	g	0.57	0.25	0.14
rs992969	A	0.75	0.85	1.1×10^{-17}	a	0.75	-0.2121	0.2645	g	0.26	0.75	0.49

Table 5. Single nucleotide polymorphisms (SNPs) associated with bronchodilator response in six independent cohort meta-analysis with p-value<$5x10^{-6}$ after linkage disequilibrium-clumping in the ancestry-stratified meta-analysis with cohort-specific results

					Stratified meta-analysis			COPD Gene		ECLIPSE		GENKOLS		TESRA		Spiromics		FHS	
Anc/Phe~	**SNP**	**Chr:Position**	**Allele**	**AF***	**Effect**	**SE**	**p-value**	**Effect**	**SE**	**Effect**	**SE**	**Effect**	**SE**	**Effect**	**SE**	**Effect**	**SE**	**Effect**	**SE**
EA FEV1	rs13262811	8:142425325	A	0.85	0.81	0.17	1.8E-06	0.51	0.23	1.61	0.57	0.95	0.65	1.78	1.10	0.34	0.52	1.37	0.39
	rs140005306	2:143707656	A	0.95	1.25	0.26	2.0E-06	0.98	0.36	3.08	0.97	1.80	0.92	1.67	1.52	0.80	0.79	1.23	0.63
	rs7315471	12:13333283	A	0.07	1.14	0.24	2.1E-06	1.25	0.33	0.79	0.90	0.11	0.95	-0.36	1.70	0.74	0.72	1.62	0.52
	rs10220877	15:38934425	A	0.17	0.73	0.16	3.2E-06	0.67	0.22	0.88	0.56	0.45	0.60	2.92	0.98	1.09	0.47	0.44	0.34
	rs76890972	16:84399755	A	0.09	1	0.22	4.7E-06	0.83	0.30	0.68	0.77	1.66	0.80	2.40	1.44	1.90	0.65	0.60	0.55
	rs72766398	2:12489567	T	0.95	1.31	0.28	3.6E-06	1.12	0.39	2.83	1.03	0.02	1.04	0.65	1.85	2.55	0.87	1.14	0.62
	rs8014708	14:101214590	A	0.1	-0.94	0.2	3.8E-06	-1.04	0.28	-0.55	0.72	-0.73	0.69	-1.58	1.34	-0.45	0.60	-1.20	0.50

EA FVC	rs7096465	10:4250500	T	0.09	0.98	0.20	1.1E-06	1.02	0.33	1.13	0.77	-0.06	0.61	2.38	1.21	0.60	0.55	1.32	0.37
	rs10894263	11:130699110	A	0.56	0.58	0.12	8.1E-07	0.63	0.19	0.12	0.45	0.30	0.40	-0.74	0.64	0.70	0.33	0.83	0.22
	rs8046017	16:84378488	A	0.57	-0.56	0.12	4.3E-06	-0.63	0.19	-0.50	0.45	-0.50	0.40	-0.29	0.64	-0.65	0.33	-0.46	0.23
	rs10020466	4:181306647	A	0.71	0.59	0.13	3.8E-06	0.50	0.21	0.96	0.50	0.62	0.44	0.76	0.75	0.39	0.36	0.68	0.23
	rs989808	4:47166781	T	0.16	0.73	0.16	2.6E-06	0.88	0.25	1.33	0.59	0.19	0.50	0.37	0.86	0.42	0.44	0.75	0.29
AA FEV1	rs116556600	21:15154158	A	0.43	-1.26	0.25	5.8E-07	-1.25	0.26	NA	NA	NA	NA	NA	NA	-1.66	1.53	NA	NA
	rs11130868	3:6249417	C	0.6	1.2	0.24	9.8E-07	1.24	0.26	NA	NA	NA	NA	NA	NA	0.84	0.73	NA	NA
	rs35870000	9:14801710	A	0.12	-1.72	0.37	3.4E-06	-1.58	0.39	NA	NA	NA	NA	NA	NA	-2.69	1.06	NA	NA
	rs2532841	10:119069842	A	0.66	1.16	0.25	4.8E-06	1.19	0.27	NA	NA	NA	NA	NA	NA	0.97	0.74	NA	NA
	rs4852100	2:240571827	A	0.76	-1.34	0.29	4.9E-06	-1.22	0.31	NA	NA	NA	NA	NA	NA	-2.26	0.86	NA	NA
	rs58795512	2:40312398	A	0.94	-2.54	0.53	1.6E-06	-2.28	0.57	NA	NA	NA	NA	NA	NA	-4.30	1.48	NA	NA
	rs491175	2:45151690	C	0.6	1.26	0.24	2.4E-07	1.26	0.26	NA	NA	NA	NA	NA	NA	1.25	0.74	NA	NA
	rs186201422	10:133458567	T	0.063	-2.85	0.62	3.7E-06	-2.85	0.62	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	rs144465006	11:18273453	A	0.077	-2.35	0.51	3.5E-06	-2.35	0.51	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	rs10426116	19:44591553	T	0.059	2.55	0.52	1.1E-06	2.31	0.55	NA	NA	NA	NA	NA	NA	4.85	1.69	NA	NA
AA FVC	rs2400730	3:135796524	A	0.29	1.53	0.29	1.6E-07	1.41	0.32	NA	NA	NA	NA	NA	NA	2.17	0.72	NA	NA
	rs10495859	2:36241146	T	0.82	-1.77	0.34	2.0E-07	-1.82	0.37	NA	NA	NA	NA	NA	NA	-1.44	0.90	NA	NA
	rs12406488	1:88071848	A	0.87	-1.8	0.39	3.7E-06	-1.87	0.43	NA	NA	NA	NA	NA	NA	-1.52	0.90	NA	NA
	rs11680558	2:11522391	A	0.086	2.68	0.56	1.4E-06	2.89	0.61	NA	NA	NA	NA	NA	NA	1.67	1.35	NA	NA
	rs41265547	2:189872891	C	0.21	1.51	0.32	1.9E-06	1.39	0.34	NA	NA	NA	NA	NA	NA	2.25	0.85	NA	NA
	rs6864533	5:20534743	T	0.093	2.43	0.48	3.3E-07	2.32	0.54	NA	NA	NA	NA	NA	NA	2.84	1.04	NA	NA
	rs1736601	6:167683260	T	0.64	1.24	0.27	3.5E-06	1.25	0.29	NA	NA	NA	NA	NA	NA	1.17	0.69	NA	NA
	rs7336381	13:114963436	A	0.77	-1.42	0.31	3.4E-06	-1.58	0.34	NA	NA	NA	NA	NA	NA	-0.65	0.74	NA	NA
	rs80202087	15:78653983	A	0.095	-2.12	0.46	4.7E-06	-2.22	0.51	NA	NA	NA	NA	NA	NA	-1.57	1.15	NA	NA
	rs1974858	16:26743681	A	0.42	-1.23	0.26	2.8E-06	-1.12	0.29	NA	NA	NA	NA	NA	NA	-1.79	0.65	NA	NA
	rs3935851	8:31133902	T	0.1	2.41	0.52	3.1E-06	2.18	0.56	NA	NA	NA	NA	NA	NA	3.90	1.41	NA	NA
	rs13437873	7:48189850	A	0.74	1.36	0.29	2.8E-06	1.22	0.32	NA	NA	NA	NA	NA	NA	2.10	0.73	NA	NA
	rs2217516	8:94401023	A	0.57	1.24	0.26	1.6E-06	1.13	0.28	NA	NA	NA	NA	NA	NA	1.85	0.66	NA	NA
	rs12713765	2:72023225	A	0.59	1.27	0.25	6.4E-07	1.31	0.28	NA	NA	NA	NA	NA	NA	1.08	0.62	NA	NA
	rs113520112	2:110362336	C	0.093	2.24	0.44	3.5E-07	2.07	0.48	NA	NA	NA	NA	NA	NA	3.21	1.14	NA	NA
	rs74491400	2:224088691	T	0.062	2.49	0.53	2.4E-06	2.48	0.57	NA	NA	NA	NA	NA	NA	2.60	1.40	NA	NA

rs28672350	4:24166929	A	0.88	1.89	0.4	2.6E-06	1.57	0.45	NA	NA	NA	NA	NA	NA	3.27	0.93	NA	NA
rs55699229	8:19114322	T	0.9	-2.25	0.47	1.7E-06	-2.25	0.47	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs144212455	15:53363818	C	0.94	-2.59	0.54	1.9E-06	-2.73	0.59	NA	NA	NA	NA	NA	NA	-1.88	1.35	NA	NA
rs199964754	18:63446314	T	0.51	1.42	0.3	2.4E-06	1.42	0.30	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Cohort abbreviations: FHS=Framingham Hear Study; COPDGene= Genetic Epidemiology of COPD; ECLIPSE=Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; TESRA=Treatment of Emphysema with a Gamma-Selective Retinoid Agonist; GenKOLS=Bergen, Norway COPD Cohort; SPIROMICS= Subpopulations and Intermediate Outcome Measures in COPD Study

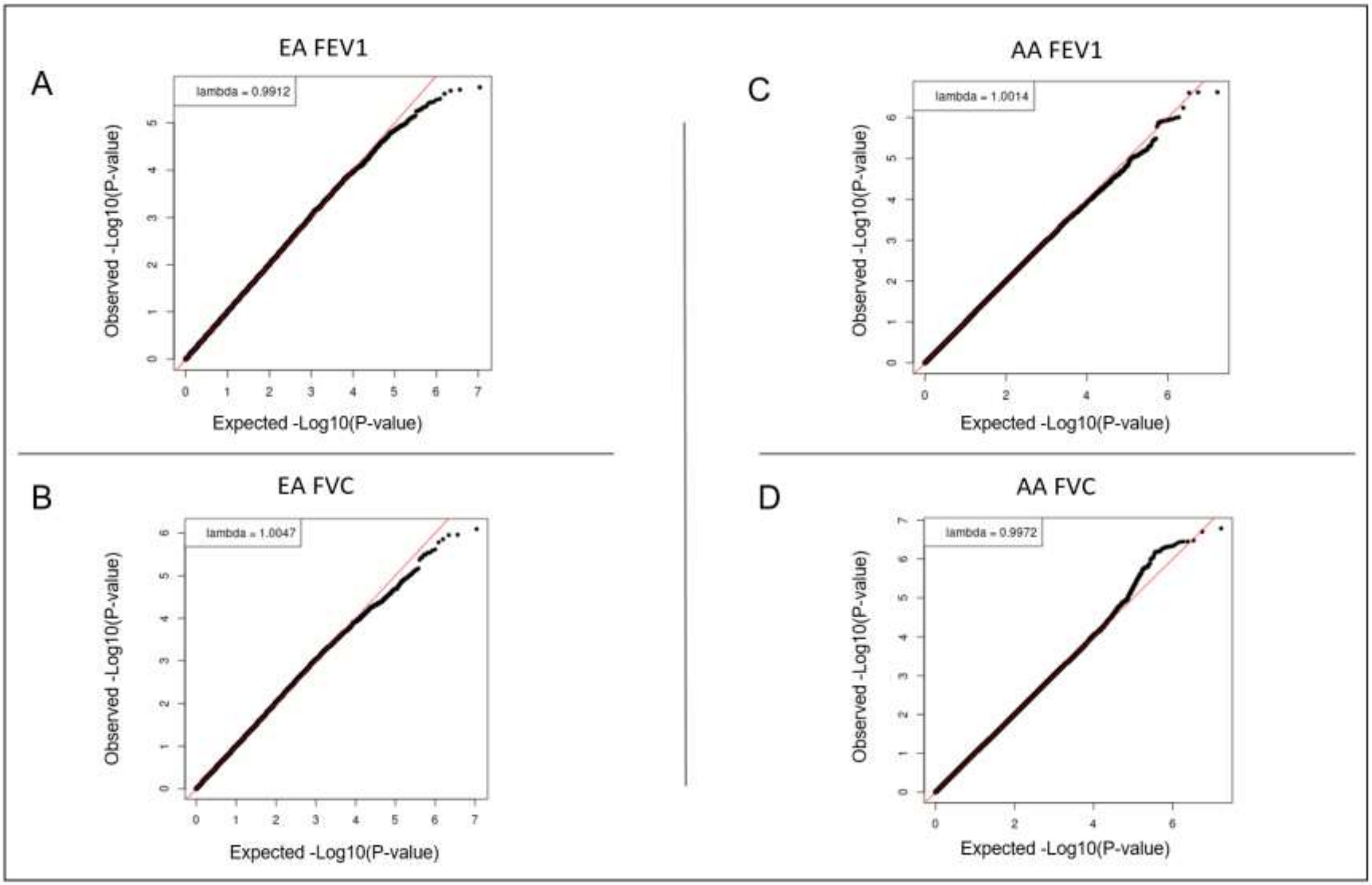

Figure S1. Quantile-Quantile (QQ) plots for GWAS of bronchodilator response (change in FEV1 or FVC in response to bronchodilators) in the stratified meta-analysis. Panels A-D denote the ancestry and phenotype: A) Change in FEV1 as percent predicted in European Ancestry (EA) participants. B) Change in FVC as percent predicted in EA participants. C) Change in FEV1 as percent predicted in African Ancestry (AA) participants. D) Change in FVC as percent predicted in AA

participants.

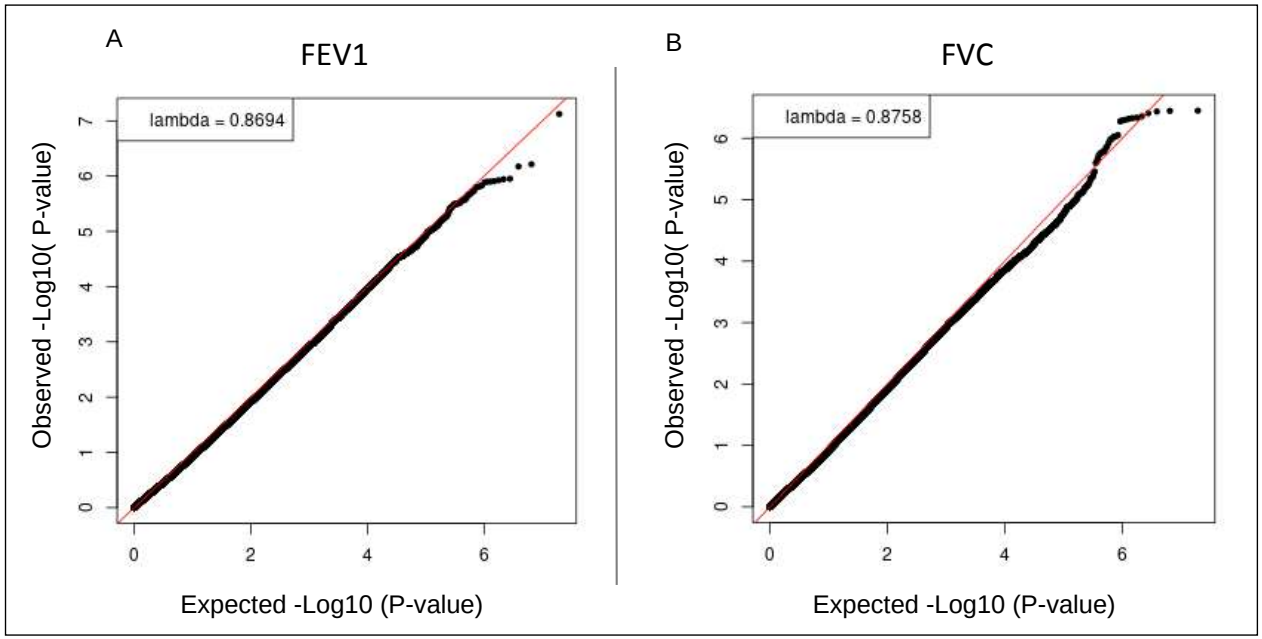

Figure S2. Quantile-Quantile (QQ) plots for GWAS of bronchodilator response (change in FEV1 or FVC in response to bronchodilators) in the combined meta-analysis. Panel A) Change in FEV1 as percent predicted in European Ancestry (EA) and African Ancestry (AA) participants; Panel B) Change in FVC as percent predicted in EA and AA participants.

References

1. Israel E, Lasky-Su J, Markezich A, Damask A, Szefler SJ, Schuemann B, et al. Genome-wide association study of short-acting β2-agonists. A novel genome-wide significant locus on chromosome 2 near ASB3. Am J Respir Crit Care Med [Internet]. 2015 Mar 1 [cited 2020 Feb 1];191(5):530–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25562107
2. Drake KA, Torgerson DG, Gignoux CR, Galanter JM, Roth LA, Huntsman S, et al. A genome-wide association study of bronchodilator response in Latinos implicates rare variants. J Allergy Clin Immunol [Internet]. 2014 Feb [cited 2020 Feb 1];133(2):370–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23992748
3. Spear ML, Hu D, Pino-Yanes M, Huntsman S, Eng C, Levin AM, et al. A genome-wide association and admixture mapping study of bronchodilator drug response in African Americans with asthma. Pharmacogenomics J [Internet]. 2019 [cited 2020 Feb 1];19(3):249–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30206298
4. Hardin M, Cho MH, McDonald M-L, Wan E, Lomas DA, Coxson HO, et al. A genome-wide analysis of the response to inhaled β2-agonists in chronic obstructive pulmonary disease. Pharmacogenomics J [Internet]. 2016 [cited 2020 Feb 1];16(4):326–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26503814
5. Mak ACY, White MJ, Eckalbar WL, Szpiech ZA, Oh SS, Pino-Yanes M, et al. Whole-Genome Sequencing of Pharmacogenetic Drug Response in Racially Diverse Children with Asthma. Am J Respir Crit Care Med [Internet]. 2018 [cited 2020 Feb 1];197(12):1552–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29509491
6. Zhao X, Qiao D, Yang C, Kasela S, Kim W, Ma Y, et al. Whole genome sequence analysis of pulmonary function and COPD in 19,996 multi-ethnic participants. Nat Commun [Internet]. 2020 Dec 1 [cited 2021 May 11];11(1). Available from: https://pubmed.ncbi.nlm.nih.gov/33057025/
7. Sakornsakolpat P, Prokopenko D, Lamontagne M, Reeve NF, Guyatt AL, Jackson VE, et al. Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. Nat Genet [Internet]. 2019 Mar 1 [cited 2021 May 12];51(3):494–505. Available from: https://pubmed.ncbi.nlm.nih.gov/30804561/
8. Cho MH, Castaldi PJ, Wan ES, Siedlinski M, Hersh CP, Demeo DL, et al. A genome-wide association study of COPD identifies a susceptibility locus on chromosome 19q13. Hum Mol Genet [Internet]. 2012 Feb [cited 2021 May 11];21(4):947–57. Available from: https://pubmed.ncbi.nlm.nih.gov/22080838/
9. Busch R, Hobbs BD, Zhou J, Castaldi PJ, McGeachie MJ, Hardin ME, et al. Genetic association and risk scores in a chronic obstructive pulmonary disease meta-analysis of 16,707 subjects. Am J Respir Cell Mol Biol [Internet]. 2017 Jul 1 [cited 2021 May 11];57(1):35–46. Available from: https://pubmed.ncbi.nlm.nih.gov/28170284/
10. Cho MH, McDonald MLN, Zhou X, Mattheisen M, Castaldi PJ, Hersh CP, et al. Risk loci for chronic obstructive pulmonary disease: A genome-wide association study and meta-analysis. Lancet Respir Med [Internet]. 2014 [cited 2021 May 12];2(3):214–25. Available from: https://pubmed.ncbi.nlm.nih.gov/24621683/

11. Demenais F, Margaritte-Jeannin P, Barnes KC, Cookson WOC, Altmüller J, Ang W, et al. Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks. Nat Genet [Internet]. 2018 Jan 22 [cited 2019 Mar 17];50(1):42–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29273806