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Common genes underlying asthma and COPD? Genome-wide analysis on the Dutch hypothesis

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Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are thought to share a genetic background ("Dutch hypothesis").

We investigated whether asthma and COPD have common underlying genetic factors, performing genome-wide association studies for both asthma and COPD and combining the results in meta-analyses.

Three loci showed potential involvement in both diseases: chr2p24.3, chr5q23.1 and chr13q14.2, containing *DDX1*, *COMMD10* (both participating in the NFκβ pathway) and *GNG5P5*, respectively. SNP rs9534578 in *GNG5P5* reached genome-wide significance after first stage replication ($p=9.96 \cdot * 10^{-9}$). The second stage replication in seven independent cohorts provided no significant replication. eQTL analysis in blood and lung on the top 20 associated SNPs identified two SNPs in *COMMD10* influencing gene expression.

Inflammatory processes differ in asthma and COPD and are mediated by NFκβ, which could be driven by the same underlying genes, *COMMD10* and *DDX1*. None of the SNPs reached genome-wide significance. Our eQTL studies support a functional role of two *COMMD10* SNPs, since they influence gene expression in both blood cells and lung tissue. Our findings either suggest that there is no common genetic component in asthma and COPD or, alternatively, different environmental factors, like lifestyle and occupation in different countries and continents may have obscured the genetic common contribution.

Introduction

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are two common respiratory diseases. Their estimated prevalence ranges from approximately 1% to 18% in different countries.[1–3] Both diseases may lead to airway obstruction, which is reversible in asthma in contrast to COPD. However, the diagnosis cannot rely on reversibility, as it can disappear with asthma progression, making asthma and COPD harder to distinguish. The immune mechanisms underlying the two diseases are thought to be very different, but similarities in inflammatory processes have recently been reported in both disease entities.[4] Classically inflammation in asthma is represented by elevated numbers of CD4+ lymphocytes and eosinophils, while in COPD there are CD8+ lymphocytes, macrophages and neutrophils.[5] However, severe asthma can be accompanied by neutrophilia [6] and COPD exacerbation by eosinophilia.[7]

Over fifty years ago, the so called 'Dutch hypothesis' was formulated by Orie and colleagues [8] stating that asthma and COPD are two features of one disease entity, referred to as chronic non-specific lung disease (CNSLD). CNSLD was defined to result from the

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interplay of endogenous factors like genetic predisposition, and exogenous factors like viral infections, air pollution, tobacco smoking and allergen exposures. The timing of this interplay would then determine which clinical syndrome one developed during a lifetime, i.e. asthma, or COPD, or features of both asthma and COPD.

So far this hypothesis has neither been confirmed nor refuted completely, [9] but several common environmental exposures have been unequivocally identified as shared risk factors for both asthma and COPD, e.g. maternal smoking during pregnancy, air pollution and active smoking.[10] Genetic factors have been associated with either asthma or COPD using linkage,[11–15] candidate gene [16–19] and genome-wide association studies (GWAS).[20,21] These studies elucidated genetic factors unique either to asthma or COPD, but additionally potentially shared genetic risk factors including *TGFB1*, *TNFA*, *GSTP1*, *IL13* [22] and *SERPINE2* [23]. *ADAM33* has been linked to the presence of asthma [24], COPD and accelerated lung function decline in the general population and in asthma [25,25], suggesting common underlying genetic factors for both onset and course of asthma and COPD.[26] So far, hypothesis free GWAS studies aiming to identify novel genes underlying both asthma and COPD in the same source population are lacking. The aim of our study was to identify shared genetic risk factors for asthma and COPD using an unbiased GWAS approach. We first performed a GWAS on asthma and COPD separately using individuals of Dutch descent and subsequently combined these in a meta-analysis, followed by 3 replication studies.

Methods

Study populations

For the identification phase, subjects were recruited as participants of the following asthma and COPD cohorts:

1. The Dutch Asthma GWAS (DAG) Study: a cohort screened for genetic studies, characterized by the presence of a doctor diagnosis of asthma and bronchial hyperresponsiveness.
2. The NELSON cohort study [42]: a population-based cohort screening for lung cancer, including current or ex-smokers with at least 20 pack-years. To increase power of the COPD set, blood bank controls from Amsterdam and Utrecht without clinical data except for age (range 18–65), were added.

The results of the GWAS were meta-analyzed (meta-analysis1). A meta-analysis is a method to combine results from different studies, with the aim to more powerfully estimate the true effect size as opposed to a less precise effect size derived in a single study. A weighted average of that common effect size is the output of a meta-analysis. The weighting is related to sample sizes within the individual studies.

For the 1st replication phase (meta-analysis2) participants of the LifeLines cohort study (LifeLines1) were studied.

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In the 2nd replication phase (meta-analyses 3–9) the top 20 single nucleotide polymorphisms (SNPs) were evaluated in participants of an independent sample of LifeLines (LifeLines2), and the SAPALDIA, RS-I, RS-II, RS-III, MESA, and ARIC cohorts.

There were no overlapping subjects in any cohorts used. All participants signed informed consent; studies were approved by institutional ethics committees. Detailed information and characteristics of the study populations are shown in Supplementary Appendix (Table S1 and Text S1).

Asthma and COPD phenotype definition

In all cohorts, asthma was defined as having a doctor diagnosis of asthma ever, or use of asthma medication (beta-agonists, steroids, anticholinergics, cromoglycate, montelukast, theophyllines) while having 2 or more of the following symptoms: wheeze without a cold, an attack of breathlessness while resting, waking up with an attack of breathlessness, ever. Controls were defined as not having asthma.

In all cohorts, COPD was defined as a pre-bronchodilator $FEV_1/FVC<0.7$ (asthma cases were excluded), and controls (except for blood bank controls) were defined as having an $FEV_1/FVC>0.7$ and $FEV_1>90\%$ predicted.

Genotyping, quality control and imputation

All cohorts were genotyped with Illumina arrays with different SNP content. Genotypes were called and standard quality control was performed (see supplement).

Study design and statistical analyses

The analytic work flow is shown in Figure 1. Genome-wide associations on asthma (2,004,043 SNPs) and COPD (1,872,289 SNPs) were performed using χ^2- test using a genetic additive model (0, 1, and 2).

Next, results were combined in a meta-analysis using 1,811,026 SNPs shared between the asthma and COPD datasets (meta-analysis1). 2,048 SNPs showing $p<0.001$ were selected for *in silico* replication in a second set of asthma and COPD case-control groups derived from the LifeLines cohort (LifeLines1). These markers were analyzed with χ^2- tests and then combined in a second directional meta-analysis (meta-analysis2). The top 20 SNPs with p 0.001 from meta-analysis2 were investigated in the second stage replication consisting of 7 meta-analyses in LifeLines2, SAPALDIA, RS-I, RS-II, RS-III, MESA, and ARIC (for cohort description see Text S1).

In the meta-analyses (apart from LifeLines 2) genetic associations with asthma and COPD were tested using logistic regression. Models were controlled for pack-years smoking, study area and principal components capturing inter-European population structure. Results were then combined using the Fisher's method. SNPs with $p<0.05$ in meta-analysis2 are shown in Table S4.

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eQTL mapping in blood and lung tissue

eQTL (expression quantitative trait locus) mapping in blood was performed as described previously by Fehrmann et al.[27] Briefly, each probe on the expression chip was mapped and correlated with SNPs in the vicinity of 250kb. Principal component analysis was applied to the data prior to the analysis to ensure that signals detected as eQTLs are not due to e.g. batch effects. Analysis involved non-parametric Spearman's rank correlation test. Because two different expression chips were used, when probes were present on both, the final result came from meta-analysis. False discovery rate was applied to account for multiple testing.

eQTL-mapping in lung tissue was performed as described previously in 3 independent data sets in a collaboration between University of Groningen (Groningen, The Netherlands), Laval University (Quebec City, Canada) and British Columbia (Vancouver, Canada).[43] Briefly lung specimens were obtained from patients undergoing lung resection surgery at the three participating sites. Whole-genome gene expression and genotyping data were obtained from these specimens. Gene expression profiling was performed using an Affymetrix custom array (GEO platform GPL10379) testing 51,627 non-control probe sets and normalized using RMA.[44] Genotyping was performed using the Illumina Human1M-Duo BeadChip array. Following standard microarray and genotyping quality controls, 1111 patients were available for eQTL analyses. *Cis*- and *trans*-acting eQTLs were calculated as previously.[45]

Network analysis

Gene network was constructed using GeneMANIA.[46] The gene set resulting from this approach was investigated with GATHER [47] to identify enriched pathways.

More details are presented in the supplement.

Results

Genome-wide association and meta-analyses

GWAS were performed on both asthma (921 cases, 3,246 controls) and COPD (1,030 cases, 1,808 controls). Genomic inflation factors (λ) equaled 1.01 for both asthma and COPD, indicating no population stratification (Figure S1). Individual p-values and odds ratios (ORs) were combined in a directional meta-analysis using a fixed-effects model (meta-analysis1, Figure 1; this data is publicly available at The European Genome-phenome Archive (EGA), accession number EGAS00000000130). All 2,048 SNPs with p 0.001 were selected for a first replication analysis in asthma (534 cases and 2,568 controls) and COPD (711 cases and 1,854 controls) cohorts separately. Subsequently results were combined in a meta-analysis (meta-analysis2, Figure 1).

Twenty SNPs replicated at $p<0.001$ (Table 2) in the combined meta-analysis1 and meta-analysis2, one SNP reached genome wide significance.

Nineteen of these 20 SNPs map to three genomic locations: 2p24.3, 5q23.1, and 13q14.2 (Table S2).

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The chromosome 2p24.3 locus spans ~380 kb and contains genes encoding functional units, like processed transcripts, pseudogenes and RNA genes (Figure 2). The nearest gene with a known function, *DEAD-box polypeptide 1* (*DDX1*), is ~139kb away from the top associated 2p24.3 SNP rs1477253. The locus on chromosome 5 is ~328 kb and contains a single gene: *COMM domain containing 10* (*COMMD10*) (Figure 2). The locus on chromosome 13 spans ~320 kb and only contains a pseudogene: *guanine nucleotide binding protein (G protein), gamma 5 pseudogene 5* (*GNG5P5*) (Figure 2). SNP rs9534578 in *GNG5P5* reached genome-wide significance ($p = 9.96*10^{-9}$).

Replication phase 2 of top 20 SNPs

The top 20 markers from the combined analysis were further evaluated in an independent sample of the LifeLines cohort (LifeLines2; asthma: 317 cases and 2,363 controls; COPD: 601 cases and 1,868 controls) and the SAPALDIA cohort (asthma: 461 cases, 522 controls, COPD: 118 cases, 656 controls), RS-I (asthma: 126 cases, 4,241 controls, COPD: 229 cases, 781 controls), RS-II (asthma: 58 cases, 1,584 controls, COPD: 186 cases, 783 controls), RS-III (asthma: 71 cases, 1,714 controls, COPD: 79 cases, 824 controls), MESA (asthma: 267 cases, 2,381 controls, COPD: 104 cases, 979 controls, COPD), ARIC (Asthma: 453 cases, 9,203 controls, COPD: 915 cases, 6,610 controls). None of the SNPs replicated at a nominal p-value <0.05. Meta-analysis of all cohorts together did not result in genome-wide significant associations (Table 2 and Forest plots of the meta-analyses of the three top SNPs in Figure 3).

SNPs in the DDX1 and COMMD10 locus were associated with both asthma and COPD (Table S3). The meta-analysis results of the GNG5P5 locus were driven by the association with the COPD phenotype, since non of the GNG5P5 SNPs were significantly associated with the asthma phenotype.

eQTL analysis of top 20 SNPs

Three of the top 20 SNPs from the combined analysis showed a *cis*-eQTL effect, when correlating the genotypes with gene expression levels in 1,469 peripheral blood mononuclear cell samples with both GWAS and genome-wide gene expression data available.[27] The three SNPs were located in *COMMD10*. Figure 4 shows that the risk allele (G) (and rs10043228 (T) which is in perfect LD (r^2=1) with rs10036292, increased *COMMD10* expression levels in blood mononuclear cells, with similar findings in lung tissue.

Network analysis

The genes found were investigated with GeneMANIA which does not support pseudogenes. Hence we queried only *COMMD10* and *DDX1*. This gene enrichment approach resulted in a set of genes, two genes (*RAD50* and *MRE11A*) being involved in regulation of mitotic recombination (Bayes factor 11, p<0.0001) and telomere maintenance (Bayes factor 6, p<0.0001), possibly implicating COPD as a disease of rapidly aging lungs. [28] Another gene (*BICD1*) involved in telomere maintenance was previously reported in emphysema. [29]

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Moreover, products of *DDX1* and *COMMD10* interact with NFκβ2. COMMD10 has a direct interaction, while DDX1 interacts with RELA and RELB, known to interact directly with NFκβ2 and to function in the same pathway (Figure 5).

Discussion

This is the first investigation of shared genetics for asthma and COPD in a hypothesis-free manner using a genome-wide screening in asthma and COPD in large population-based cohorts. We report three novel loci as potentially shared genetic factors between asthma and COPD, none reaching genome-wide significance in the discovery set or seven replication cohorts. None of these three loci were previously reported to be associated with either asthma or COPD. However, *DDX1* locus was reported in a recently published meta-analysis of lung function [30], with a p-value of $9*10^{-6}$. The T allele of rs2544527 in *DDX* was associated with lower lung function and in our study with a risk for both asthma and COPD.

The shared 5q23.1 risk locus contains the *COMMD10* gene. COMMD10 is a member of COMM domain containing proteins [31] with a largely unknown function. COMMD10 has been shown to form a complex with COMMD1, another member of this family of proteins, which regulates copper metabolism and sodium uptake and inhibits NFκβ activation.[32] Copper and sodium levels are inversely regulated, i.e. when copper levels increase, sodium import in cells is inhibited and vice versa. Both ion levels can be regulated by COMMD1, with sodium control mediated through epithelial sodium channels (ENaCs) that are abundantly present in lung epithelial cells.[33] Sodium is crucial for maintaining a fluidic layer in the alveolar part of the lungs and ENaCs play a crucial role in this process.[34] It is tempting to speculate that COMMD10 is involved in this maintenance either through interaction with COMMD1, or independently by displaying similar functions as COMMD1. Also, its function in inhibition of NFκβ activation could play a role in regulating inflammatory processes in airways diseases. Our eQTL studies support a functional role of *COMMD10*, since we established that two SNPs in the *COMMD10* region influence expression of this gene in both blood cells and lung tissue.

The 13q14.2 locus contains the guanine nucleotide binding protein (G protein), gamma 5 pseudogene 5 (*GNG5P5*). Poliseno et al recently showed that pseudogenes can have a pronounced role in regulation of their putative transcripts by competing in non-coding RNA binding.[35] It needs to be tested whether *GNG5P5* can affect GNG5 levels, but it is interesting to note that the pseudogene is processed and has a transcript (ENST00000420444). The biological consequence of a change in GNG5 levels in relation to asthma and COPD pathology is unclear but it is well established that G proteins play a crucial role in signal transduction from cell surface to its interior. It is also known that G-protein coupled receptors (GPCRs) are involved in asthma and more generally are a target of many of the currently used asthma drugs.[36]

A third locus on 2p24.3 is bordered by the *DDX1* gene, encoding DEAD-box protein 1, RNA helicase I, and the *MYCN* genes whereas the locus itself contains non-protein coding genes including lincRNAs, ncRNAs, pseudogenes, processed transcripts and one newly discovered, protein-coding gene. Theoretically, any of these could be involved in asthma

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and COPD, hindering interpretation of our findings. However, the regional association plot (Figure 2) shows that the signal is mostly confined to *AC008278.3* and *AC008271.1*. Further refinement of the region and functional assessment of the associated variants could help to potentially pin-point the actual causal gene. *DDX1* is a plausible candidate for both asthma and COPD since it interacts with RELA, one of NFκβ subunits, upon which it acts as a co-activator of NFκβ-mediated transcription.[37] Since this is a central and common pathway of inflammation present in the airways of both asthma and COPD, this may signify a unifying underlying mechanism of both disease entities. Further studies are needed to confirm this hypothesis.

The strengths of our study are the data quality of the cohorts involved, the design of the study and the analysis strategy of the discovery and replication phases. There are some limitations to our study as well. We found no overall replication in 6 out of 8 replication cohorts. One explanation for the lack of replication might be the differences in asthma and COPD patients in the replication cohorts compared with the identification cohort. For instance there was a somewhat lower prevalence of asthma in LifeLines2 (7.5% versus 8.5% in LifeLines1) due to the average older age of the subjects included in LifeLines2. This could reflect a cohort effect or some asthma remission at elderly ages.[38] Furthermore, most studies used an asthma definition of self-reported asthma diagnosis. Self-reported asthma has led to firm GWAS findings in the GABRIEL study.[39] However, it cannot be excluded that our asthmatic groups consisted in part of individuals diagnosed with asthma in childhood, who now are in complete remission. The GABRIEL cohort studies [39] suggested that the genetic background of early onset and adult-onset asthma is different. It would be of interest to assess whether COPD would have more overlap in genetic background with either childhood-onset than adult-onset asthma. A previous study from our group (48) showed overlap between candidate genes for COPD and early childhood wheeze and lower lung function, suggesting there is some overlap in genetic background in early childhood characteristics. This clearly needs further study, since we could not analyze this adequately in our cohort, where the prevalence of childhood asthma was 82% in our identification cohort and 41 in the verification cohort. Similarly, the diagnosis of COPD was based on lung function only, and this could have led to inclusion of different types of COPD in the various replication cohorts. For instance the prevalence of never smokers was 41% in SAPALDIA, whereas this was 0% in the identification and LifeLines 1 and 2 cohorts and ranging from 10–24% in the other cohorts. Furthermore some cohorts were of older age (e.g. mean age around 65 years in RS-I and RS-II and this may have led to inclusion of elderly asthmatics in the COPD group, since significant persistent airway obstruction may occur in asthma with ageing.[40] This may reflect an important limitation common to most GWAS, i.e. the heterogeneity of the phenotypes assessed, and heterogeneity between discovery and replication samples. Table S3 shows the heterogeneity per meta-analysis performed, i.e. for each asthma-COPD meta-analysis. It differs substantially and due to specificity of the study we could not account for the heterogeneity between meta-analyses. We did not find as prime hits a gene that was associated with asthma and with COPD previously. For instance *ADAM33* was not significantly associated with either asthma or COPD or represented in their overlap. This may either be due to the fact that not all SNPs were captured in the GWAS analyses, or that *ADAM33* was only found by positionally cloning when

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hyperresponsiveness was present in asthmatics (49). The latter was not a prerequisite in our asthma definition, just as in other GWAS studies, where *ADAM33* was also not found as a significant gene associated with asthma.

Do our findings then refute the Dutch hypothesis? This hypothesis states that both genetic and environmental factors contribute to the phenotypic outcome, and that there is a common genetic background. Indeed the current study did not find significant genetic similarities between asthma and COPD apart from the identification cohort and LifeLines1. As highlighted by the Dutch hypothesis the importance of both type and temporal sequences of environmental exposures contribute to the occurrence of either phenotype. This may have affected the phenotypic outcome considerably and hence a crude covariate adjustment may represent an underestimated challenge to identify common genetic determinants of asthma and COPD. Finally, our study has power to identify strongly prevalent SNPs, yet not rare variants that may have an impact on asthma and COPD. Our findings either suggest that there is no common genetic component in asthma and COPD or, alternatively, different environmental factors, like lifestyle and occupation in different countries and continents may have obscured the genetic common contribution.

Recent efforts to characterize substantial number of patients diagnosed with both asthma and COPD [41] show the increasing scientific interest in the phenotypic overlap between asthma and COPD. Future studies on the underlying genetics in this group of overlap patients would be of interest, specifically comparing outcomes with our results. Overall, our results may suggest a role of the NFκβ pathway, a key transcription factor in the inflammatory response, in both asthma and COPD, suggesting that the Dutch hypothesis may have some validity. However, we could not replicate associations in both asthma and COPD in most replication cohorts, thus this could refute the genetic background that the Dutch hypothesis implied to be common in asthma and COPD. Further studies including lifelong lifestyle factors across all cohorts need to be performed to assess whether this approach elucidates a common genetic background of asthma and COPD. Since none of the SNPs reached genome-wide significance further investigation of the loci should be performed to assess their role in both asthma and COPD. Although inflammatory processes differ in asthma and COPD, they are unequivocally mediated by NFκβ, and as suggested by our current results, they could be driven by the same underlying genes, *COMMD10* and *DDX1*. Our eQTL studies support a functional role of *COMMD10*, since we established that two SNPs, therefore the natural next step is to perform genome-wide epistatic analysis in large cohorts of asthma and COPD patients to reveal the complex nature of interactions between SNPs and loci and their impact on the ultimate phenotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Take home message

This article provides suggestive evidence, but not firm evidence that there is overlap in genetics of asthma and COPD.

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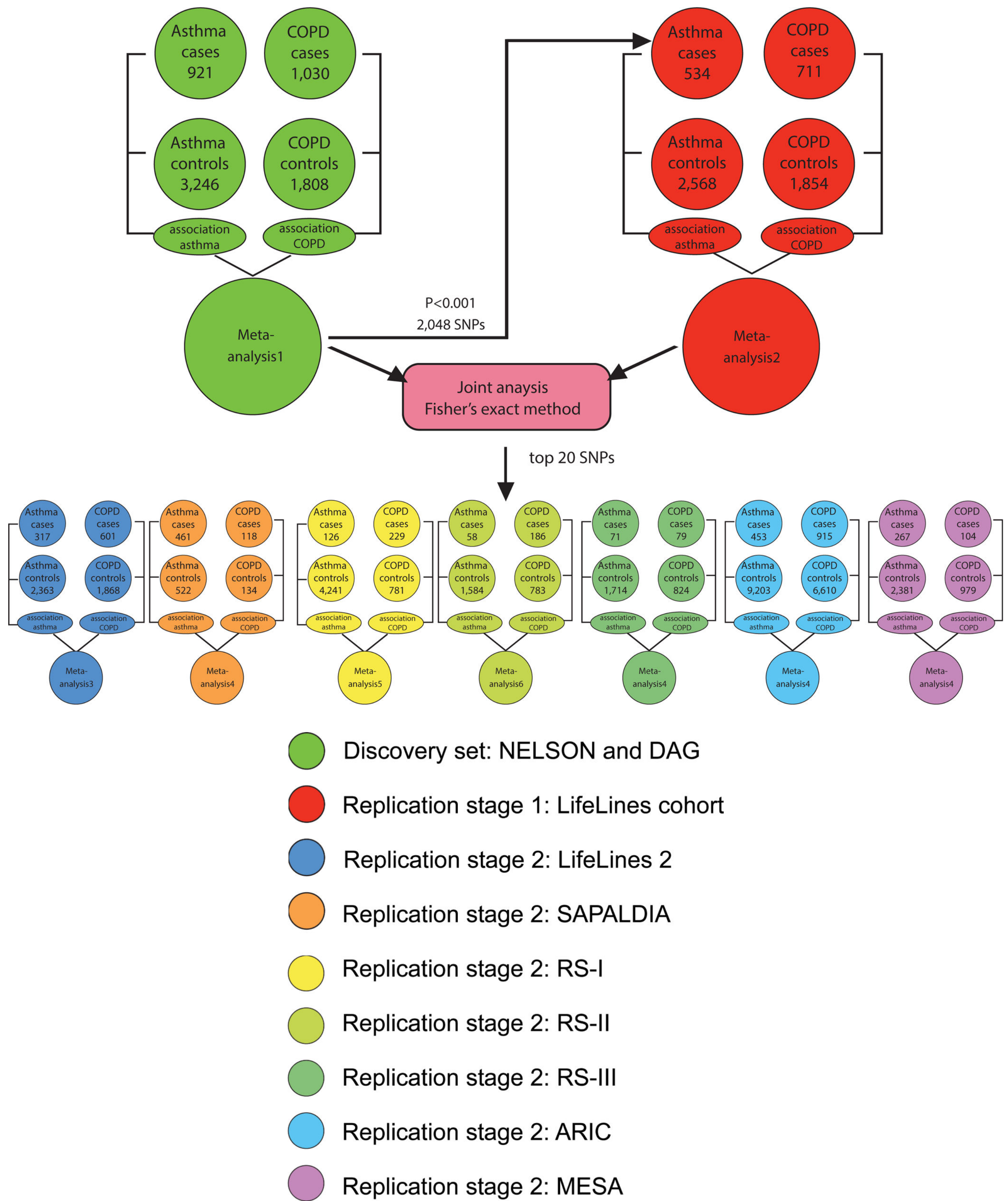

Figure 1.

Analytic work flow

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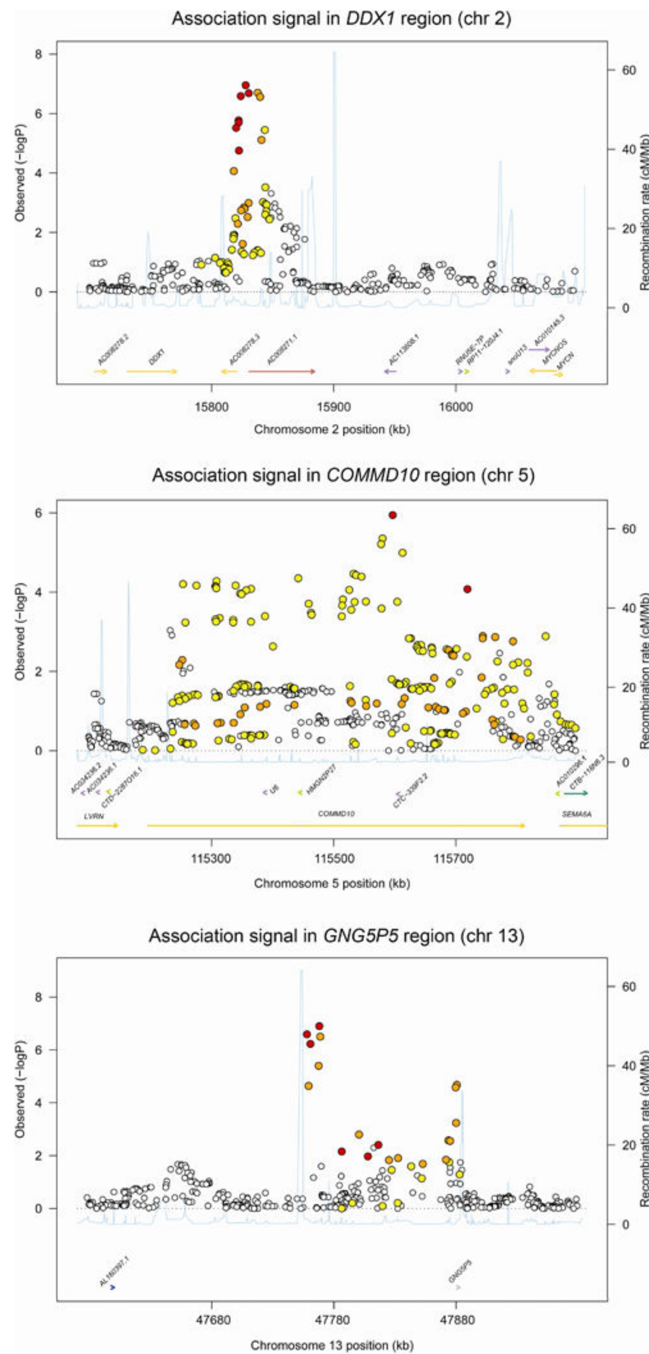

Figure 2.

Regional association plots for *DDX1*, *COMMD10* and *GNG5P5* loci.

The plots were generated using R and regional association plot script from BROAD institute

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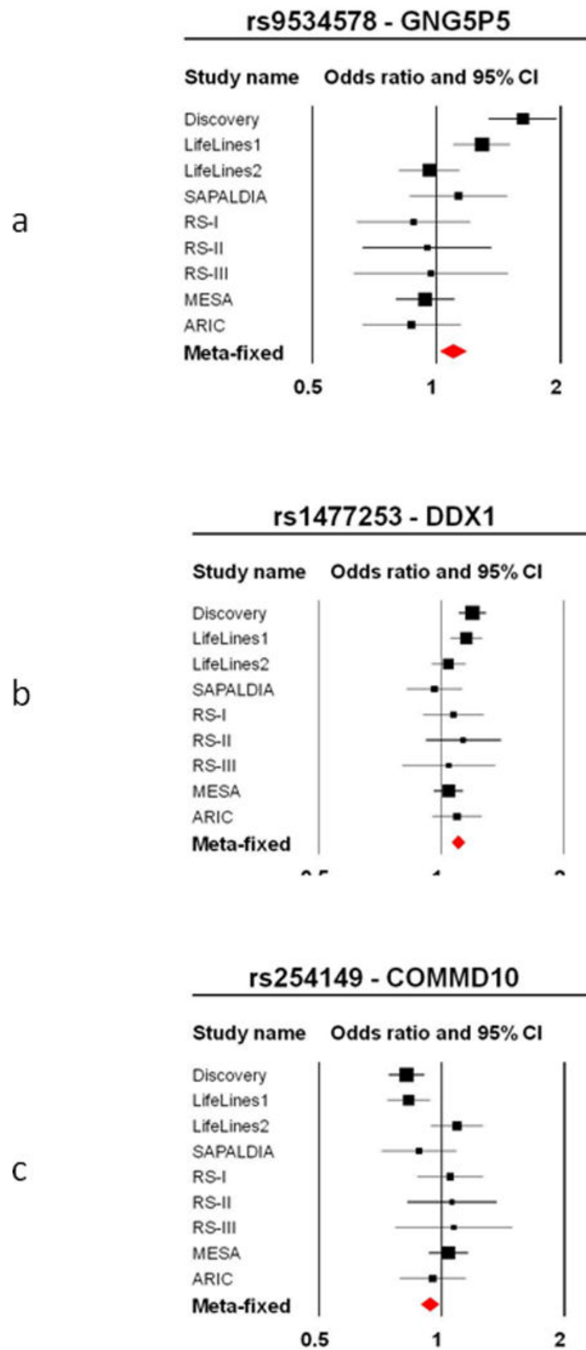

Figure 3.

Forest plots of the three top SNPs in the meta-analysis of the asthma and COPD cohorts.

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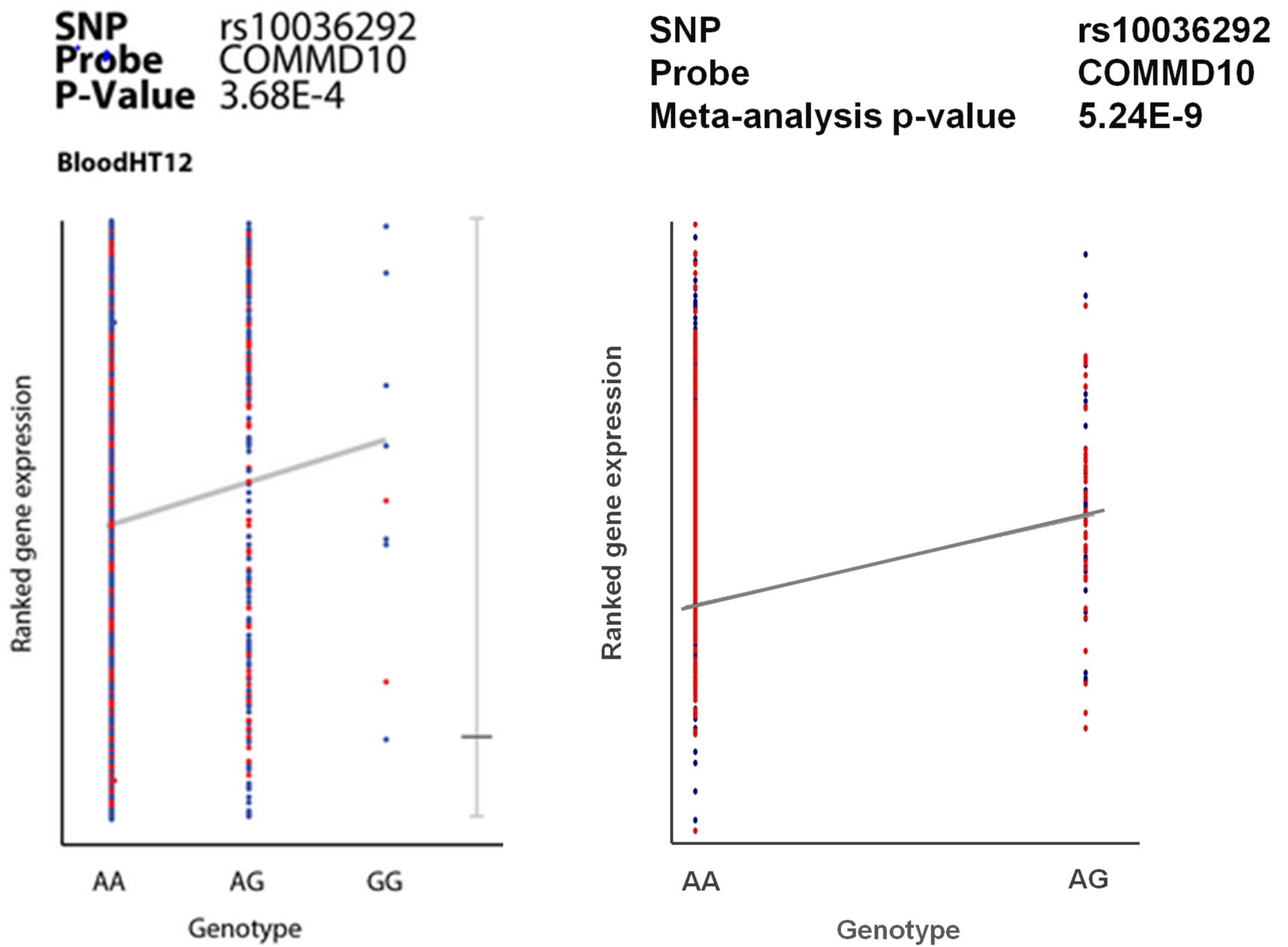

Figure 4.

eQTLs identified for *COMMD10* SNPs.

Left panel: blood eQTLs, right panel: lung eQTLs. Order on x-axis is from non-risk homozygote, heterozygote and risk homozygote for all three eQTLs. Note: in lung tissue dataset, the risk homozygotes were not present.

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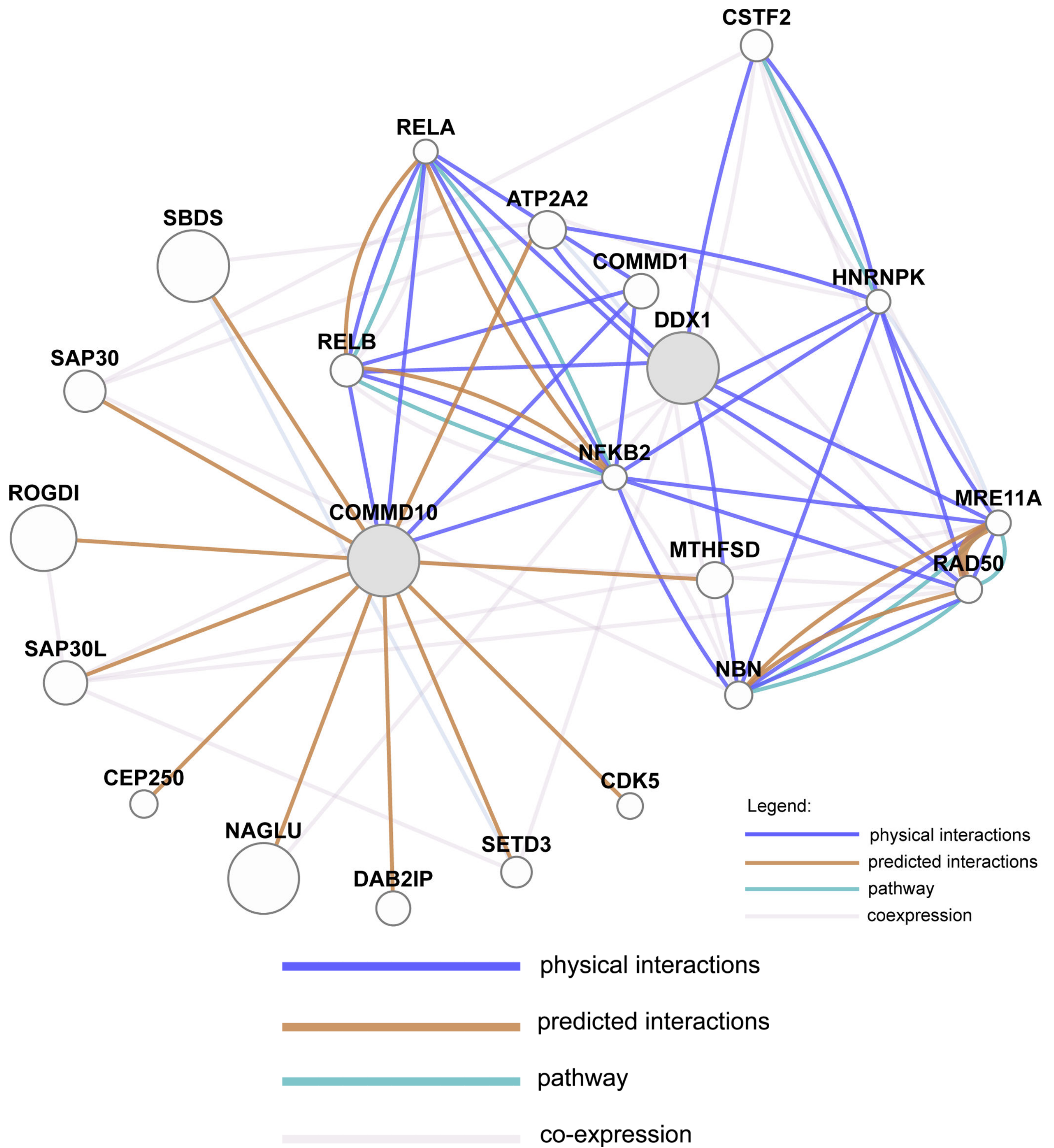

Figure 5.
Gene enrichment plot using *DDX1* and *COMMD10* genes as a query

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Table 1

shows the characteristics of the identification and replication cohorts.

	Phenotype	N	Age, yrs, mean (SD)	Gender male n (%)	Current smoker, n (%)	Never smoker, n (%)	Ex smoker, n (%)	Pack-years, median (p25 – p75)*
DAG	asthma	920	34 (16)	430 (47)	147 (16.0)	544 (59.1)	226 (24.6)	7.9 (2.1 –17.3)
	controls	2.777	55.4 (9.9)	991 (36)	396 (14)	1,305 (47)	1076 (39)	1.95 (0–11.6)
NELSON	COPD	1.030	63.3 (5.6)	1,030 (100)	410 (39.8)	0 (0)	620 (60.2)	38.7 (29.7–49.5)
	controls	844[a]+964[b]	59.1 (5)	964 (100)	64,4	0 (0)	35,5	34.2 (27.9–46.2)
LifeLines1	asthma	534	44.8 (9.7)	214 (40)	106 (19.9)	293 (54.9)	135 (25.3)	10.8 (4.9 –20.5)
	controls	2.568	43 (9.4)	1,102 (42.9)	266 (10.4)	2,010 (78.8)	276 (10.8)	12.75 (5.5–20.4)
	COPD	711	54 (10.6)	369 (52)	363 (51.1)	0 (0)	348 (48.9)	16.8 (8.5 –26.7)
	controls	1.854	43.2 (8.6)	807 (43.5)	805 (43.4)	0 (0)	1049 (56.6)	9 (4–15)
LifeLines2	asthma	317	46.7 (11.2)	120 (37.9)	41(12.9)	171(53.9)	105 (33.1)	7.4 (3 – 15.5)
	controls	2.363	48.5 (11.6)	885 (37.5)	165 (7.2)	1922 (83.3)	220 (9.5)	12 (5–20.5)
	COPD	601	56.7 (10.8)	282 (46.9)	231(38.4)	0 (0)	370 (61.6)	15.2(7 – 25.2)
	controls	1.868	49.6 (10.9)	784 (42.0)	601 (32.2)	0 (0)	1267 (67.8)	8.6 (4–16)
SAPALDIA2	asthma	461	49.0 (11.8)	212 (46.0)	95 (20.6)	215 (46.6)	151 (32.8)	16.3 (4.9–32.9)
	controls	522	51.4 (11.1)	244 (46.7)	95 (18.2)	252 (48.3)	175 (33.5)	13.1 (5.1–25.5)
	COPD	118	58.3 (10.0)	67 (56.8)	44 (37.3)	49 (41.5)	25 (21.2)	37.0 (15.4–52.7)
	controls	134	51.4 (10.4)	60 (44.8)	30 (22.4)	68 (50.8)	36 (26.9)	14.8 (3.9–27.0)
RS-I	asthma	126	65.8 (7.8)	33 (26.2)	24 (19)	50 (40)	51 (41)	15.4 (4.5–37.4)
	controls	4.241	69.8 (9.2)	1,499 (35.3	782 (18)	1,854 (44)	1,605 (38)	20 (7.5–37.5)
	COPD	229	79.8 (4.9)	126 (55)	51 (22)	36 (16)	142 (62)	26 (9.8–45)
	controls	781	79.1 (4.5)	306 (39)	49 (6)	299 (38)	433 (55)	16.8 (5.7–36.0)
RS-II	asthma	58	62.9 (6.8)	15 (26)	7 (12)	23 (40)	28 (48)	21.6 (6–43.8)
	controls	1.584	64.7 (8.0)	712 (45)	249 (16)	526 (33)	809 (51)	14 (3.6–31)
	COPD	186	72.8 (5.1)	108 (58)	48 (26)	28 (15)	110 (59)	31.7 (16.4–46.0)
	controls	783	72.1 (4.9)	327 (42)	52 (7)	317 (41)	415 (53)	13.9 (3.7 –28.0)
RS-III	asthma	71	54.7 (4.5)	20 (28)	6 (9)	27 (38)	38 (54)	15.5 (1.2–25.7)

	Phenotype	N	Age, yrs, mean (SD)	Gender male n (%)	Current smoker, n (%)	Never smoker, n (%)	Ex smoker, n (%)	Pack-years, median (p25 – p75)*
	controls	1.714	55.8 (5.6)	764 (45)	356 (21)	574 (34)	784 (46)	13.8 (4.0–29.0)
	COPD	79	56.9 (5.0)	40 (51)	32 (41)	19 (24)	28 (35)	28.9 (16.2–44.7)
	controls	824	56.5 (5.5)	353 (43)	137 (17)	288 (35)	399 (48)	12.5 (3.8–26.6)
	asthma	453	54.3 (5.8)	226 (50)	107 (23.62)	181 (39.96)	165 (36.42)	29.6 (14.1–45.0)
	controls	9.203	54.8 (5.7)	4,318 (47)	2,268 (24.64)	3,691 (40.11)	3,239 (35.20)	26.0 (12–40)
	COPD	915	55.6 (5.57)	506 (55)	522 (57.1)	93 (10.2)	300 (32.8)	39 (29–54)
ARIC	controls	6.610	54.1 (5.67)	3,042 (46)	1,120 (16.9)	3,096 (46.8)	2394 (36.2)	20.3 (9–34)
	asthma	267	61.1 (9.6)	119 (45)	29 (11)	112 (58)	124 (47)	20 (6–41.3)
	controls	2.381	63.0 (10.2)	1149 (48)	263 (11)	1,061 (55)	1,053 (44)	19 (6.6–37.8)
	COPD	104	67.1 (8.9)	51 (49)	19 (18)	15 (14)	70 (67)	37 (22–64)
MESA	controls	979	66.0 (10.0)	467 (48)	55 (6)	446 (46)	478 (49)	17.3 (7–36)

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Table 2

Top 20 SNPs resulting from the identification meta-analysis1 and 1st phase replication meta-analysis2.

					Meta1		Meta2			Meta3		Meta4		Meta5		Meta6		Meta7		Meta8		Meta9		Overall	
CHR	BP	SNP	LOCUS	A1	P	OR	P	OR	META1+2	P	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P_replication	Poverall
2	15820130	rs2112101	DDX1	T	1.32E-04	1.16	5.42E-03	1.14	3.01E-06	0.44	1.04	0.54	0.95	0.38	1.08	0.34	1.11	0.89	1.02	0.45	1.04	0.32	1.09	0.68	2.90E-05
2	15822156	rs6728667	DDX1	G	1.64E-04	1.16	2.67E-03	1.15	1.68E-06	0.31	1.06	0.37	0.92	0.34	1.09	0.24	1.14	0.72	1.05	0.60	1.02	0.37	1.08	0.53	1.32E-05
2	15822185	rs6728750	DDX1	G	1.01E-04	1.16	4.57E-03	1.14	1.99E-06	0.36	1.05	0.49	0.94	0.41	1.08	0.23	1.14	0.74	1.04	0.57	1.03	0.07	1.16	0.36	1.10E-05
2	15823917	rs2544534	DDX1	T	3.14E-05	1.18	1.78E-03	1.16	2.56E-07	0.42	1.04	0.47	0.94	0.42	1.07	0.26	1.13	0.72	1.05	0.40	1.04	0.22	1.11	0.52	2.23E-06
2	15827908	rs1477253	DDX1	T	7.28E-06	1.19	2.52E-03	1.15	1.11E-07	0.43	1.04	0.61	0.96	0.44	1.07	0.26	1.13	0.77	1.04	0.35	1.04	0.31	1.09	0.61	1.18E-06
2	15830470	rs2693008	DDX1	G	1.78E-05	1.19	2.26E-03	1.15	2.06E-07	0.40	1.05	0.85	0.98	0.36	1.08	0.14	1.17	0.68	1.05	0.38	1.04	0.69	1.03	0.64	2.23E-06
2	15837774	rs2544523	DDX1	T	2.39E-05	1.18	1.74E-03	1.16	1.98E-07	0.22	1.07	0.67	1.04	0.54	1.06	0.05	1.23	0.55	1.08	0.13	1.07	0.95	1.01	0.30	1.04E-06
2	15839739	rs2693019	DDX1	T	2.85E-05	1.18	2.04E-03	1.16	2.74E-07	0.22	1.07	0.64	1.04	0.53	1.06	0.05	1.23	0.55	1.08	0.14	1.07	0.91	1.01	0.29	1.36E-06
2	15840892	rs1363058	DDX1	C	1.28E-04	1.16	1.25E-02	1.12	7.66E-06	0.25	1.06	0.97	1.00	0.53	1.06	0.01	1.32	0.20	1.18	0.22	1.06	0.91	0.99	0.14	1.60E-05
2	15843619	rs2544527	DDX1	T	5.07E-05	1.18	1.23E-02	1.13	3.54E-06	0.19	1.07	0.79	0.98	0.26	1.11	0.18	1.16	0.63	1.07	0.18	1.06	0.57	1.05	0.36	1.85E-05
5	115623770	rs10036292	COMMD10	G	4.04E-04	0.78	4.27E-03	0.75	6.12E-06	0.26	1.12	0.41	0.88	0.82	1.03	0.68	1.08	0.83	0.95	2.47E-04	1.32	0.60	0.93	**0.05**	**4.99E-06**
5	115624947	rs10043228	COMMD10	T	3.43E-04	0.78	3.58E-03	0.75	4.41E-06	0.29	1.11	0.40	0.87	0.84	1.03	0.66	1.08	0.82	0.95	2.55E-04	1.32	0.60	0.93	**0.05**	**3.84E-06**
5	115633819	rs254149	COMMD10	G	9.76E-05	0.82	2.81E-03	0.83	1.13E-06	0.25	1.09	0.24	0.88	0.61	1.05	0.65	1.06	0.69	1.07	0.49	1.04	0.59	0.95	0.71	1.20E-05
5	116557808	rs7718941	RP11-535A15.1	C	7.32E-05	1.30	2.09E-02	0.74	9.12E-06	0.43	1.13	0.09	0.82	0.68	1.05	0.08	0.76	0.61	0.92	0.88	0.99	0.26	0.88	0.29	3.69E-05
13	46725490	rs7985155	GNG5P5	G	8.38E-07	1.60	1.81E-02	1.24	2.55E-07	0.61	0.93	0.31	0.87	0.33	0.86	0.82	0.96	0.88	0.97	0.45	0.94	0.40	0.88	0.79	3.31E-06
13	46728991	rs4391953	GNG5P5	C	8.78E-07	1.60	3.18E-02	1.22	5.88E-07	0.92	0.99	0.30	1.15	0.34	0.86	0.83	0.96	0.83	0.95	0.49	0.95	0.44	0.89	0.86	7.80E-06
13	46737339	rs17069785	GNG5P5	G	3.20E-05	1.42	1.80E-02	1.20	3.97E-06	0.12	0.87	0.30	0.88	0.10	0.78	0.83	0.96	0.97	1.01	0.18	0.91	0.76	0.96	0.34	1.95E-05
13	46738025	rs17069787	GNG5P5	A	1.58E-06	1.58	7.51E-03	1.27	1.25E-07	0.98	1.00	0.23	1.18	0.42	0.88	0.80	0.95	0.78	0.94	0.47	0.95	0.43	0.89	0.84	1.79E-06
13	46739001	rs7994542	GNG5P5	T	3.29E-05	1.31	2.06E-03	1.22	3.13E-07	0.96	1.00	0.96	0.99	0.18	0.84	0.53	0.91	0.94	1.01	0.03	0.87	0.58	0.94	0.53	2.77E-06
13	46741378	rs9534578	GNG5P5	A	6.17E-07	1.62	1.81E-03	1.29	9.96E-09	0.64	0.96	0.38	1.13	0.43	0.88	0.78	0.95	0.89	0.97	0.46	0.94	0.32	0.87	0.83	1.62E-07

[*] A1 is a minor allele and the risk allele

[†] A2 is a major allele

[‡] MAF is minor allele frequency; calculated in the discovery sample