Supplemental Materials

Genotype Data

In order to be included in a meta-analysis, studies needed to present data either in the form of allelic or genotypic contrasts. When data were reported as genotypes, the allelic table was calculated from the genotypes. Studies reporting data solely as odds ratios were entered in the database but not included in meta-analyses.

Duplicate Publications

Two issues regarding duplicate populations were taken into account in our analysis and database design. First, some case or control groups likely were represented in multiple publications. If two or more publications shared an author and had a similar number of cases and/or controls with similar baseline characteristics, then these studies were considered to have been performed on the same population. For analyses of study population characteristics we excluded duplicate reports of the same study population, and in instances where a study population appeared to be a subset of a larger population from another publication, we counted only the larger study population.

Second, if association data for the same variant were reported from the same study population or a subset of the same population in multiple publications, then data from the largest study was entered and all other data was reported as "NA" and the study was designated as "overlaps with X" where X is the name of the largest study.

Genetic Variant Naming Issues

We extracted variant names as they were used in the original publication, and we attempted to map each variant to an rs number. For variants in which the rs number was not reported, variant names were typically reported as amino acid substitutions, DNA substitutions, microsatellites, or insertion/deletions. We used the following algorithm to attempt to identify an rs number: 1.) We searched dbSNP using data presented on gene, genetic location (i.e. intron 4, etc..), nucleotide substitution or amino acid substitution. 2.) If rs assignment was still ambiguous, we used the reported primer data and the "in-silico PCR" function of the UCSC genome browser to generate sequence data which we then queried against the dbSNP database using BLAST. If primer data was not included in the original publication, or if the rs assignment remained ambiguous, we used the variant name as reported in the initial publication. In our database, each variant is linked to its corresponding rs number, DNA substitution, amino-acid change, and any other name used to refer to this variant in any publication. For cases in which there were naming discrepancies (i.e. slight changes in DNA position based on multiple transcription start sites), a single name was chosen to organize each variant, but the other names were maintained as aliases.

Comparison with Previous Meta-Analyses

We compared our results with the results obtained by previous COPD meta-analytic efforts. In cases in which studies used different genetic models or fixed-effect meta-analyses methods, we repeated our analysis using the methods of each study to confirm that we could reproduce their results. In instances in which a large number of analyses were reported in a single paper, we reproduced the first analysis reported in a

table or figure. We did not reproduce analyses in which multiple alleles were grouped by putative function (i.e. EPHX1 fast vs slow variant).

Supplementary Table 1. Genes Included in Database

Gene	Chromosome	Comparisons**
ACE	17	6
ADAM33	20	8
ADRB2	5	11
BDKRB2	14	1
CAT	11	2
CD63	12	3
CDKN1A	6	1
CFTR	7	3
CLCA1	1	8
CYP1A1	15	2
CYP2D6	22	1
CYP2E1	10	5
DCN	12	5
DEFB1	8	3
ELN	7	1
EPHX1	1	30
GABPA	21	4
GC	4	2
GCLC	6	1
GSTMI	1	8
GSTP1	11	12
GSTT1	22	5
HLA-B	6	NA*
HMOX1	22	NA*
HOXA11	7	NA*
HSPA1A	6	1
HSPA1B	6	1
HSPA1L	6	1
IL10	1	4
IL11	19	NA*
IL13	5	9
IL17F	6	1
IL1B	2	10
IL1RN	2	2
IL4	5	11
IL6	7	3
IL8	4	4
LTA	6	2
MBL2	10	1
MICB	6	1
MMP1	11	2

MMP14	14	12
MMP2	16	1
MMP9	20	6
MRPL44	2	NA*
MS4A2	11	NA*
MSR1	8	5
NOS3	7	5
OGG1	3	1
PDE4D	5	6
SCGB1A1	11	1
SERPINA1	14	NA*
SERPINA3	14	12
SERPINE2	2	8
SFTPA1	10	NA*
SFTPB	2	3
SFTPD	10	2
SLC6A4	17	3
SOD1	21	1
SOD2	6	2
SOD3	4	3
TGFB1	19	14
TGFB2	1	1
TIMP2	17	6
TLR4	9	1
TLR6	4	1
TNF	6	49
TNFRSF1A	12	1
TNFRSF1B	1	1
TP53	17	1
VDR	12	2
VEGFA	6	2

* NA - data not available because polymorphisms not biallelic or studies excluded for other cause.
** Distinct case-control comparisons.

Supplementary Table 2: Meta-Analysis Results Obtained When Excluding Studies in which Data are Reported for Multiple Study Populations (i.e. more than 1 case-control comparison).

Gene	Polymorphism	rs number	Contrast	OR	Studies*	Studies Removed?
ACE	indel		del --> ins	1.02 (0.80-1.30)	4	Yes
ADRB2	+46 AG	rs1042713	A to G	1.17 (0.69-1.97)	3	Yes
ADRB2	+79 CG	rs1042714	C to G	1.32 (0.91 -1.93)	3	Yes
EPHX1	His139Arg	rs2234922	A to G	1.06 (0.90-1.25)	13	Yes
EPHX1	Tyr113His	rs1051740	C to T	1.12 (0.94-1.33)	13	Yes
GSTP1	Ile105Val	rs1695	A to G	1.09 (0.80-1.48)	10	No
IL13	+2044 GA		A to G	NA	2	Yes
IL13	-1055 CT		C to T	NA	1	Yes
IL1B	-31 TC		C to T	NA	2	Yes
IL1B	-511 CT		C to T	1.80 (1.35-2.39)	3	Yes
IL4	-33 CT	rs2070874	C to T	NA	2	Yes
IL6	-174 GC		C to G	NA	1	Yes
LTA	+252 AG		A to G	NA	2	Yes
MMP9	-1562 CT		C to T	0.69 (0.44-1.09)	4	No
SERPINA3	Ala9Thr		A to G	0.80 (0.62-1.03)	5	No
SOD3	Arg213Gly	rs1799895	C to G	NA	1	Yes
TGFB1	-509 CT	rs1800469	C to T	1.05 (0.70-1.58)	4	No
TGFB1	+29 TC	rs1800470	C to T	0.76 (0.64-0.88)	3	Yes
TIMP2	+853 GA	rs2277698	A to G	0.59 (0.23-1.48)	3	No
TNF	+489 GA	rs1800610	A to G	NA	2	Yes
TNF	-1031 TC	rs1799964	C to T	NA	1	Yes
TNF	-238 GA	rs361525	A to G	0.79 (0.50-1.25)	3	Yes
TNF	-308 GA	rs1800629	A to G	1.05 (0.91-1.21)	11	Yes
TNF	-857 CT	rs1799724	C to T	NA	1	Yes
TNF	-863 CA	rs1800630	A to C	NA	2	Yes
GSTM1	null		null --> wt	1.45 (1.09-1.92)	8	No
GSTT1	null		null --> wt	0.92 (0.73-1.15)	5	No

* Number of case-control comparisons in which a variant has been tested for association with COPD.

Supplementary Table 3: Meta-Analysis Results Obtained without Dividing Cases and Controls by the Number of Duplicate Contrasts to Avoid Double-Counting

Gene	Polymorphism	rs number	Contrast	OR	Studies*
ACE	indel		del --> ins	1.16 (0.96-1.40)	6
ADRB2	+46 AG	rs1042713	A to G	1.11 (0.75-1.65)	5
ADRB2	+79 CG	rs1042714	C to G	0.89 (0.51-1.41)	5
EPHX1	His139Arg	rs2234922	A to G	1.06 (0.91-1.22)	15
EPHX1	Tyr113His	rs1051740	C to T	1.11 (0.95-1.29)	15
GSTP1	Ile105Val	rs1695	A to G	1.09 (0.80-1.48)	10
IL13	+2044 GA		A to G	1.03 (0.80-1.33)	4
IL13	-1055 CT		C to T	0.73 (0.35-1.50)	3
IL1B	-31 TC		C to T	0.95 (0.65-1.40)	4
IL1B	-511 CT		C to T	1.42 (0.96-2.10)	5
IL4	-33 CT	rs2070874	C to T	1.07 (0.81-1.40)	4
IL6	-174 GC		C to G	0.97 (0.75-1.24)	5
LTA	+252 AG		A to G	1.00 (0.82-1.22)	4
MMP9	-1562 CT		C to T	0.69 (0.44-1.09)	4
SERPINA3	Ala9Thr		A to G	0.80 (0.62-1.03)	5
SOD3	Arg213Gly	rs1799895	C to G	2.22 (1.32-3.75)	3
TGFB1	-509 CT	rs1800469	C to T	1.05 (0.70-1.58)	4
TGFB1	+29 TC	rs1800470	C to T	0.72 (0.63-0.82)	5
TIMP2	+853 GA	rs1800610	A to G	0.59 (0.23-1.48)	3
TNF	+489 GA	rs1800610	A to G	1.22 (0.94-1.59)	6
TNF	-1031 TC	rs1799964	C to T	0.86 (0.67-1.10)	3

TNF	-238 GA	rs361525	A to G	0.84 (0.58-1.22)	5
TNF	-308 GA	rs1800629	A to G	1.21 (1.03-1.43)	27
TNF	-857 CT	rs1799724	C to T	1.02 (0.79-1.31)	3
TNF	-863 CA	rs1800630	A to C	0.87 (0.66-1.14)	3
GSTM1	null		null --> wt	1.45 (1.09-1.92)	8
GSTT1	null		null --> wt	0.92 (0.73-1.15)	5
* Number of case-control comparisons in which a variant has been tested for association with COPD.					

Search Strategy Used for Ovid Database Search - Search conducted July 16, 2008.

1. copd.mp. or exp Pulmonary Disease, Chronic Obstructive/

2. emphysema.mp. or exp Emphysema/ or exp Pulmonary Emphysema/

3. chronic bronchitis.mp. or exp Bronchitis, Chronic/

4. chronic obstructive pulmonary disease.mp.

5. exp Forced Expiratory Volume/ or fev1.mp.

6. 1 or 2 or 3 or 4 or 5

7. gene.mp. or exp Genes/

8. exp Genetics, Population/ or exp "Variation (Genetics)"/ or exp "Enhancer Elements (Genetics)"/ or Genetic.mp. or exp "Antisense Elements (Genetics)"/ or exp "Trans-Activation (Genetics)"/ or exp Genetics/ or exp "Operator Regions (Genetics)"/ or exp

"Selection (Genetics)"/ or exp "Terminator Regions (Genetics)"/ or exp "Linkage (Genetics)"/ or exp Genetics, Behavioral/ or exp "Promoter Regions (Genetics)"/ or exp Genetics, Medical/

9. genotype.mp. or exp Genotype/

10. allele.mp. or exp Alleles/

11. polymorphism.mp. or exp Polymorphism, Restriction Fragment Length/ or exp Polymorphism, Single-Stranded Conformational/ or exp Polymorphism, Genetic/ or exp Polymorphism, Single Nucleotide/

12. haplotype.mp. or exp Haplotypes/

13. exp "Linkage (Genetics)"/ or linkage.mp. or exp Linkage Disequilibrium/

14. exp Chromosome Mapping/ or exp Genetic Predisposition to Disease/ or exp "Linkage (Genetics)"/ or genome wide scan.mp. or exp Genome, Human/ or exp Lod Score/

15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16. 6 and 15

17. limit 16 to (humans and english language)

18. limit 17 to "review articles"

19. 17 not 18