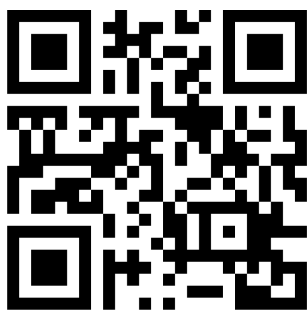


# Updates on the COPD gene list

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**Abstract:** A genetic contribution to develop chronic obstructive pulmonary disease (COPD) is well established. However, the specific genes responsible for enhanced risk or host differences in susceptibility to smoke exposure remain poorly understood. The goal of this review is to provide a comprehensive literature overview on the genetics of COPD, highlight the most promising findings during the last few years, and ultimately provide an updated COPD gene list. Candidate gene studies on COPD and related phenotypes indexed in PubMed before January 5, 2012 are tabulated. An exhaustive list of publications for any given gene was looked for. This well-documented COPD candidate-gene list is expected to serve many purposes for future replication studies and meta-analyses as well as for reanalyzing collected genomic data in the field. In addition, this review summarizes recent genetic loci identified by genome-wide association studies on COPD, lung function, and related complications. Assembling resources, integrative genomic approaches, and large sample sizes of well-phenotyped subjects is part of the path forward to elucidate the genetic basis of this debilitating disease.

**Keywords:** COPD, genetics, lung function, candidate genes, genome-wide association study

## Introduction

Chronic obstructive pulmonary disease (COPD) is the third-leading cause of worldwide mortality and is predicted to remain a major public health problem in the near future.<sup>1,2</sup> It is characterized by airflow limitations that occur in approximately 10% of adults aged  $\geq 40$  years.<sup>3</sup> Cigarette smoking is the primary risk factor. However, only a fraction of smokers (~20%) develop the disease, and host differences in susceptibility are thus persuasive. The author has previously reviewed the genetics of COPD and COPD-related phenotypes.<sup>4</sup> The current review aims to: (1) update this publication, (2) provide a comprehensive literature overview on the genetics of COPD, (3) highlight the most promising findings during the last few years, and ultimately (4) provide an updated COPD gene list.

## Chronic obstructive pulmonary disease candidate-gene studies

A systematic review of the literature was conducted in order to provide a comprehensive overview of genes associated with COPD and related phenotypes. PubMed was searched using the string “genetics and COPD” on January 5, 2012. All titles and abstracts were reviewed for inclusion. The goal was to obtain all publications testing genetic variants in humans for association with COPD and related phenotypes (ie, spirometric

measurements, emphysema, chronic bronchitis, lung-function decline, etc). Population-based, case-control, and family studies were included. The author attempted to include all reported articles without quality assessment or exclusion criteria based on sample size or other criteria. The search for relevant publications was complemented using the list of references in relevant manuscripts and the COPD genetic association compendium.<sup>5</sup> Readers are welcome to contact the author for any articles missed in the current review.

A large number of candidate gene–association studies were conducted to identify the COPD-susceptibility genes. Table 1 provides a comprehensive overview of the genes associated with COPD and related phenotypes using this genetic approach. Supplementary Table 1 presents additional genes tested but showing lack of association with COPD and related phenotypes. Most genes in these tables were studied because of their potential role in the pathobiology of COPD, but some also represent follow-up genes originally identified from genome-wide linkage and association studies. Genes are presented in alphabetical order. Single studies and meta-analyses testing each gene are indicated. An attempt was made to classify each article as supportive or not of a given gene based on the conclusions provided by the authors. Single genetic markers, haplotypes, or combinations of variants associated with COPD, COPD severity, COPD-related phenotypes, or complications were considered as positives. Table 1 aims to provide an exhaustive list of publications for any given gene.

A total of 192 genes are summarized in Table 1 and Supplementary Table 1. Figure 1 illustrates these genes based on the number of publications supporting the association with COPD phenotypes. Briefly, 86 genes are supported by one study, 36 genes by two to five studies, 15 genes by six to ten studies, and seven genes by more than ten studies. The latter seven genes include *ADRB2*, *TGFB1*, *TNF*, *GSTM1*, *GSTP1*, *SERPINA1*, and *EPHX1*. Note that Figure 1 must be interpreted with caution. Replication of genotype–phenotype associations is the gold standard to identify genes conferring susceptibility.<sup>6</sup> However, the number of supportive studies is not necessarily an indication that a gene is consistently replicated. Figure 2 illustrates the relationship between the number of studies supporting and not supporting the list of COPD genes. It seems that genes replicated many times in COPD are simply the most popular genes studied. For example, the author found 20 studies supporting *TNF* as a COPD-susceptibility gene. However, lack of association between this gene and COPD phenotypes was found in 20 other studies (Table 1). Considering publication bias, candidate genes

associated with COPD are not consistently replicated and the overall results are rather inconclusive. In fact, excluding *SERPINA1* (encoding the alpha-1 antitrypsin protein), none of the other genes are well-proven susceptibility genes for COPD. Perhaps the most convincing candidate COPD genes up to now are those less studied but consistently replicated, such as *SOD3*. Many of the most studied COPD genes have now been investigated in meta-analyses.

## Meta-analyses

A number of meta-analyses have been conducted to identify genes robustly associated with COPD and lung function. So far, meta-analyses have been conducted for genes involved in the following pathways: inflammation (*IL4*, *IL6*, *IL13*, *IL1B*, *IL1RN*, *LTA*, *TNF*, and *TGFB1*), protease/antiprotease (*MMP9*, *TIMP2*, and *SERPINA3*), oxidative stress (*GSTM1*, *GSTP1*, *GSTT1*, *EPHX1*, *SOD2*, and *SOD3*), and others (*ACE* and *ADRB2*). These studies and their main outcomes are summarized by gene in Table 1. Among these genes, *GSTM1* was consistently associated with COPD in more than one meta-analysis.<sup>5,7,8</sup> This is also true for *TNF*, but only in Asian populations.<sup>5,8–11</sup> In contrast, other genes have not been supported in meta-analyses conducted so far, including *GSTT1*,<sup>5,7,8</sup> *IL1B*,<sup>5,8</sup> *IL6*,<sup>5,8</sup> and *MMP9*.<sup>5,8</sup> The other genes considered in meta-analyses were either reported in only one study or showed conflicting results across studies (Table 1).

As genetic data accumulates, more genes and polymorphisms will be considered in meta-analyses. Combining the findings of an increasing number of studies will allow pooled analyses in more homogenous subgroups based on ethnicity, smoking history, emphysema vs airway type of COPD, and others. These subgroup analyses are likely to be important in finding susceptibility genes for COPD. Ongoing activities gathering genetic data in the field of COPD are important. For example, a web application summarizing candidate-gene studies was recently established.<sup>5</sup> At the time of publication, this database included 108 genetic-association studies, including population-based and case-control studies but excluding family-based studies. Seventy-two genes were studied, focusing strictly on single-marker biallelic polymorphisms. A total of 27 genetic variants were found to be reported in three or more independent study populations and summarized into a meta-analysis. Four genes were found to carry a single genetic variant significantly associated with COPD, being *GSTM1*, *TGFB1*, *TNF*, and *SOD3*. It should be noted that this COPD genetic-association compendium has not been updated since April 2010 and does not included

**Table 1** List of genes associated with chronic obstructive pulmonary disease

Symbol	Name	Chromosome	References			
			Single studies		Meta-analyses	
			Positive	Negative	Positive	Negative
<i>A2M</i>	Alpha-2-macroglobulin	12	51			
<i>ABCC1</i>	ATP-binding cassette, sub-family C (CFTR/MRP), member 1	16	52–54			
<i>ACE</i>	Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	17	55–60	61,62		5
<i>ADAM33</i>	ADAM metalloproteinase domain 33	20	63–68	69,70		
<i>ADRB2</i>	Adrenergic, beta-2-, receptor, surface	5	71–82	83		5,83
<i>ALOX5AP</i>	Arachidonate 5-lipoxygenase-activating protein	13	84			
<i>AQP5</i>	Aquaporin 5	12	85,86			
<i>BCL2</i>	B-cell CLL/lymphoma 2	18	87			
<i>BDKRB2</i>	Bradykinin receptor B2	14	88			
<i>CASP10</i>	Caspase 10, apoptosis-related cysteine peptidase	2	89			
<i>CAT</i>	Catalase	11	90	91,92		
<i>CCL5</i> ( <i>RANTES</i> )	Chemokine (C-C motif) ligand 5	17	93	79		
<i>CCR2</i>	Chemokine (C-C motif) receptor 2	3	94			
<i>CD14</i>	CD14 molecule	5	95,96			
<i>CD40</i>	CD40 molecule, TNF receptor superfamily member 5	20	97			
<i>CD63</i>	CD63 molecule	12	98			
<i>CD86</i>	CD86 molecule	3	99			
<i>CDC6</i>	Cell division cycle 6 homolog ( <i>S cerevisiae</i> )	17	100			
<i>CDKN1A</i> ( <i>p21</i> )	Cyclin-dependent kinase inhibitor 1A (p21, Cip1)	6	101			
<i>CFTR</i>	Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)	7	102–108	109,110		
<i>CHI3L1</i>	Chitinase 3-like 1 (cartilage glycoprotein-39)	1	111			
<i>CHRNA3</i>	Cholinergic receptor, nicotinic, alpha 3 (neuronal)	15	26,30,31, 112,113			
<i>CHRNA5</i>	Cholinergic receptor, nicotinic, alpha 5 (neuronal)	15	26,30,31, 112,113			
<i>CLCA1</i>	Chloride channel accessory 1	1	114			
<i>COL4A3</i>	Collagen, type IV, alpha 3 (Goodpasture antigen)	2	115			
<i>CRP</i>	C-reactive protein, pentraxin-related	1	116	117–119		
<i>CSF2</i>	Colony stimulating factor 2 (granulocyte-macrophage)	5	120	121		
<i>CSF3</i>	Colony stimulating factor 3 (granulocyte)	17	121			
<i>CTLA4</i>	Cytotoxic T-lymphocyte-associated protein 4	2	99,122,123			
<i>CTSS</i>	Cathepsin S	1	124			
<i>CYBA</i>	Cytochrome b-245, alpha polypeptide	16	125			
<i>CYP1A1</i>	Cytochrome P450, family 1, subfamily A, polypeptide 1	15	125–128	129,130		
<i>CYP1A2</i>	Cytochrome P450, family 1, subfamily A, polypeptide 2	15	129,131	125,128		
<i>CYP2E1</i>	Cytochrome P450, family 2, subfamily E, polypeptide 1	10	127,132	130		
<i>CYP2F1</i>	Cytochrome P450, family 2, subfamily F, polypeptide 1	19	133			
<i>CYP3A5</i>	Cytochrome P450, family 3, subfamily A, polypeptide 5	7	134			
<i>DEFB1</i>	Defensin, beta 1	8	135,136	137		
<i>DEFB4A</i>	Defensin, beta 4A	8	138			
<i>EDN1</i>	Endothelin 1	6	139–141	142,143		
<i>EDNRB</i>	Endothelin receptor type B	13	143			

(Continued)

Table 1 (Continued)

Symbol	Name	Chromosome	References			
			Single studies		Meta-analyses	
			Positive	Negative	Positive	Negative
<i>ELN</i>	Elastin (supravalvular aortic stenosis, Williams–Beuren syndrome)	7	144,145	146,147		
<i>EPHX1</i>	Epoxide hydrolase 1, microsomal (xenobiotic)	1	77,83,130,146–167	127,168–174	175	5,8,176
<i>ESR1</i>	Estrogen receptor 1	6	177			
<i>FAM13A</i>	Family with sequence similarity 13, member A	4	26			
<i>FGF10</i>	Fibroblast growth factor 10	5	178			
<i>GC</i>	Group-specific component (vitamin D binding protein)	4	179–186	146,147,151,155,187		
<i>GCLC</i>	Glutamate-cysteine ligase, catalytic subunit	6	188	172,189		
<i>GCLM</i>	Glutamate-cysteine ligase, modifier subunit	1	190	172,188		
<i>GSTCD</i>	Glutathione S-transferase, C-terminal domain containing	4	191			
<i>GSTM1</i>	Glutathione S-transferase M1	1	127,148,161,164,165,192–202	90,130,146,147,151,169,203–206	5,7,8	
<i>GSTO1</i>	Glutathione S-transferase omega 1	10	207			
<i>GSTO2</i>	Glutathione S-transferase omega 2	10	207			
<i>GSTP1</i>	Glutathione S-transferase pi 1	11	77,90,146,148,151,152,157,164,165,193,194,196,204,208–210	69,127,130,147,149,159,171,185,197,203,211,212	8,213	5,214
<i>GSTT1</i>	Glutathione S-transferase theta 1	22	127,165,193,196–198,204–206	90,130,148,161,164,169,194,199–201,203		5,7,8
<i>HCK</i>	Hemopoietic cell kinase	20	215			
<i>HHIP</i>	Hedgehog interacting protein	4	26,191,216			
<i>HLA</i>	Classical class II subregion of the MHC	6	217,218	219,220		
<i>HMOX1</i>	Heme oxygenase (decycling) 1	22	130,151,166,221–224	69,147,185,196,225		
<i>HTR4</i>	5-hydroxytryptamine (serotonin) receptor 4	5	191			
<i>IFNG</i>	Interferon, gamma	12	226–228			
<i>IL1A</i>	Interleukin 1, alpha	2	227			
<i>IL1B</i>	Interleukin 1, beta	2	227,229–233	120,228,234–238		5,8
<i>IL1RN</i>	Interleukin 1 receptor antagonist	2	231,232,234,235	228,230,236–238	8	
<i>IL2</i>	Interleukin 2	4	227			
<i>IL27</i>	Interleukin 27	16	239			
<i>IL4</i>	Interleukin 4	5	71,227,240	120,241,242		5
<i>IL4R</i>	Interleukin 4 receptor	16	227,243	79,241		
<i>IL5</i>	Interleukin 5 (colony-stimulating factor, eosinophil)	5	244			
<i>IL6</i>	Interleukin 6	7	118,228,234,245–247	116,233,236,248		5,8
<i>IL8</i>	Interleukin 8	4	120	234,235,238,249,250		
<i>IL8RA</i>	Interleukin 8 receptor, alpha	2	251	120,146,147		
<i>IL8RB (CXCR2)</i>	Interleukin 8 receptor, beta	2	250	120,146,147		
<i>IL10</i>	Interleukin 10	1	149,227,235,248,252–254	120,234,255		
<i>IL12B</i>	Interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40)	5	227	239		

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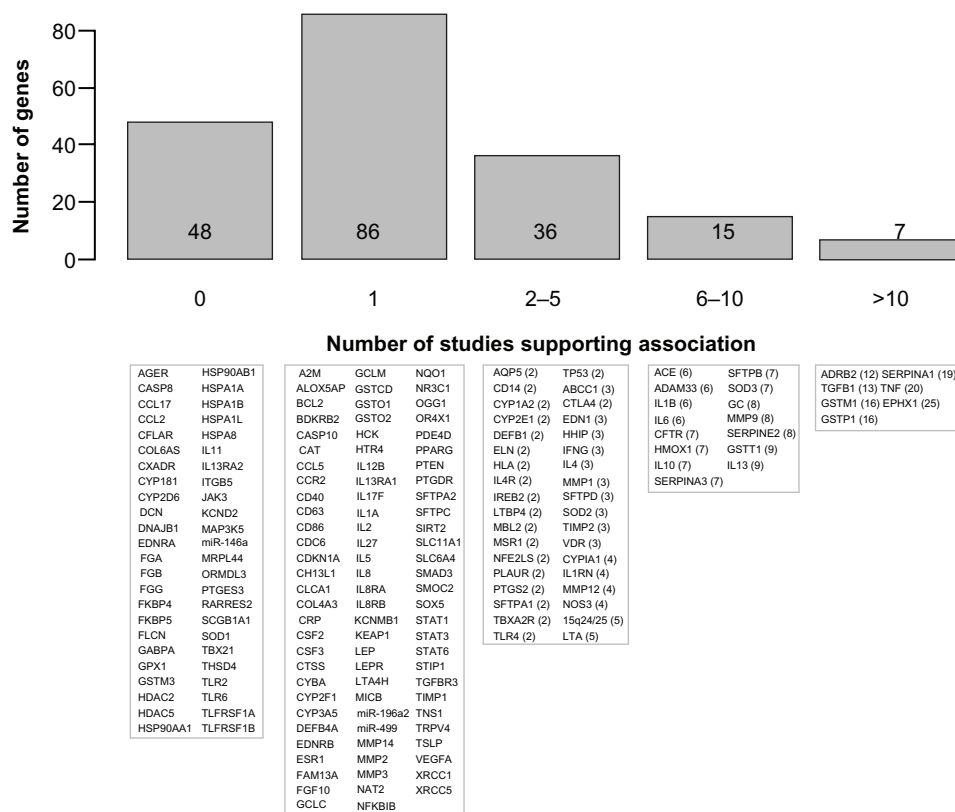
Table 1 (Continued)

Symbol	Name	Chromosome	References			
			Single studies		Meta-analyses	
			Positive	Negative	Positive	Negative
<i>IL13</i>	Interleukin 13	5	79,241,242, 256–261	71,120,238, 243,262		5
<i>IL13RA1</i>	Interleukin 13 receptor, alpha 1	X	241			
<i>IL17F</i>	Interleukin 17F	6	263			
<i>IREB2</i>	Iron-responsive element binding protein 2	15	26,30,47			
<i>KCNMB1</i>	Potassium large conductance calcium-activated channel, subfamily M, beta member 1	5	264			
<i>KEAP1</i>	Kelch-like ECH-associated protein 1	19	265			
<i>LEP</i>	Leptin	7	266			
<i>LEPR</i>	Leptin receptor	1	267			
<i>LTA</i>	Lymphotoxin alpha (TNF superfamily, member 1)	6	234,268–272	120,233,248, 273–275		5
<i>LTA4H</i>	Leukotriene A4 hydrolase	12	84			
<i>LTBP4</i>	Latent transforming growth factor beta binding protein 4	19	146,147			
<i>MBL2</i>	Mannose-binding lectin (protein C) 2, soluble	10	276,277			
<i>MICB</i>	MHC class I polypeptide-related sequence B	6	278			
<i>MIR196A2</i>	MicroRNA 196a-2	12	279			
<i>MIR499A</i>	MicroRNA 499a	20	279			
<i>MMP1</i>	Matrix metalloproteinase 1 (interstitial collagenase)	11	146,280,281	69,128,147, 151,282–285		
<i>MMP2</i>	Matrix metalloproteinase 2 (gelatinase A, 72 kDa gelatinase, 72 kDa type IV collagenase)	16	285	69,281		
<i>MMP3</i>	Matrix metalloproteinase 3 (stromelysin 1, progelatinase)	11	286	128,287		
<i>MMP9</i>	Matrix metalloproteinase 9 (gelatinase B, 92 kDa gelatinase, 92 kDa type IV collagenase)	20	128,202,281, 282,284, 288–290	69,147,151, 280,283,285,287		5,8
<i>MMP12</i>	Matrix metalloproteinase 12 (macrophage elastase)	11	280,283, 291,292	69,146,147, 282,284, 285,287		
<i>MMP14</i>	Matrix metalloproteinase 14 (membrane-inserted)	14	293			
<i>MSR1</i>	Macrophage scavenger receptor 1	8	137,294			
<i>NAT2</i>	N-acetyltransferase 2 (arylamine N-acetyltransferase)	8	132			
<i>NFE2L2</i>	Nuclear factor (erythroid-derived 2)-like 2	2	265,295			
<i>NFKB1B</i>	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, beta	19	185			
<i>NOS3</i>	Nitric oxide synthase 3 (endothelial cell)	7	57,62, 296,297	149		
<i>NQO1</i>	NAD(P)H dehydrogenase, quinone 1	16	90			
<i>NR3C1</i>	Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	5	298	299		
<i>OGG1</i>	8-oxoguanine DNA glycosylase	3	300	189		
<i>OR4X1</i>	Olfactory receptor, family 4, subfamily X, member 1	11	301			
<i>PDE4D</i>	Phosphodiesterase 4D, cAMP-specific (phosphodiesterase E3 dunce homolog, drosophila)	5	302			
<i>PLAUR</i>	Plasminogen activator, urokinase receptor	19	303,304			
<i>PPARG</i>	Peroxisome proliferator-activated receptor gamma	3	163			
<i>PTEN</i>	Phosphatase and tensin homolog	10	14			
<i>PTGDR</i>	Prostaglandin D2 receptor (DP)	14	305			
<i>PTGS2</i> ( <i>COX2</i> )	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	1	306,307			
<i>SERPINA1</i>	Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	14	76,308–325	326–336		

(Continued)

Table 1 (Continued)

Symbol	Name	Chromosome	References			
			Single studies		Meta-analyses	
			Positive	Negative	Positive	Negative
<i>SERPINA3</i>	Serpin peptidase inhibitor, clade A (alpha-1 antitrypsin, antitrypsin), member 3	14	337–343	146,147,149, 151,310,314, 326,332,344		5
<i>SERPINE2</i>	Serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2	2	77,146,149, 326,345–348	147,152,171, 349,350		
<i>SFTPA1</i>	Surfactant protein A1	10	69,351			
<i>SFTPA2</i>	Surfactant protein A2	10	69			
<i>SFTPB</i>	Surfactant protein B	2	147,151,171, 351–354	69,77,146, 149,152,355		
<i>SFTPC</i>	Surfactant protein C	8	356	357		
<i>SFTPD</i>	Surfactant protein D	10	69,358,359	151,351		
<i>SIRT2</i>	Sirtuin 2	19	185			
<i>SLC6A4</i>	Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	17	360			
<i>SLC11A1</i>	Solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1	2	361			
<i>SMAD3</i>	SMAD family member 3	15	362			
<i>SMOC2</i>	SPARC related modular calcium binding 2	6	363			
<i>SOD2</i>	Superoxide dismutase 2, mitochondrial	6	364–366	91,92,271		8
<i>SOD3</i>	Superoxide dismutase 3, extracellular	4	90,91,364, 367–370		5	8
<i>SOX5</i>	SRY (sex determining region Y)-box 5	12	371			
<i>STAT1</i>	Signal transducer and activator of transcription 1, 91 kDa	2	185			
<i>STAT3</i>	Signal transducer and activator of transcription 3 (acute-phase response factor)	17	372			
<i>STAT6</i>	Signal transducer and activator of transcription 6, interleukin-4 induced	12	79	241		
<i>STIP1</i>	Stress-induced-phosphoprotein 1	11	373			
<i>TBXA2R</i>	Thromboxane A2 receptor	19	244,374			
<i>TGFB1</i>	Transforming growth factor, beta 1	19	69,77,146, 147,238, 375–382	30,149,151, 171,383	5,8	384
<i>TGFB3</i>	Transforming growth factor, beta receptor III	1	190			
<i>TIMP1</i>	TIMP metalloproteinase inhibitor 1	X	285	69		
<i>TIMP2</i>	TIMP metalloproteinase inhibitor 2	17	146,385,386	147,151,387		5
<i>TLR4</i>	Toll-like receptor 4	9	388,389	96,271		
<i>TNF</i>	Tumor necrosis factor (TNF superfamily, member 2)	6	11,149,151, 234,238,250, 262,268, 270–272, 390–398	83,120,146, 147,155,230, 233,235–237, 248,269, 273–275, 399–403	5,8–11	
<i>TNSI</i>	Tensin 1	2	191			
<i>TP53</i> (p53)	Tumor protein p53	17	101,307			
<i>TRPV4</i>	Transient receptor potential cation channel, subfamily V, member 4	12	404			
<i>TSLP</i>	Thymic stromal lymphopoietin	5	405			
<i>VDR</i>	Vitamin D (1,25-dihydroxyvitamin D3) receptor	12	406–408	409		
<i>VEGFA</i>	Vascular endothelial growth factor A	6	410	411		
<i>XRCC1</i>	X-ray repair complementing defective repair in Chinese hamster cells 1	19	300			
<i>XRCC5</i>	X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining)	2	412			



**Figure 1** Candidate genes associated with chronic obstructive pulmonary disease (COPD) or related phenotypes.

**Notes:** The upper part shows a histogram of the number of COPD susceptibility genes based on the number of publications supporting a significant genetic association. The lower part shows the corresponding genes in each bar. Official gene symbols are indicated. The number of publications that are supportive is indicated in parentheses. References are provided in Table 1 for genes supported by at least one publication and in Supplementary Table 1 for genes tested but not supported.

more recent genetic studies on COPD. Updating this type of resource is important to draw reliable conclusions about the contribution of genes. The number of studies for most COPD-susceptibility genes is currently insufficient to reach firm conclusions.

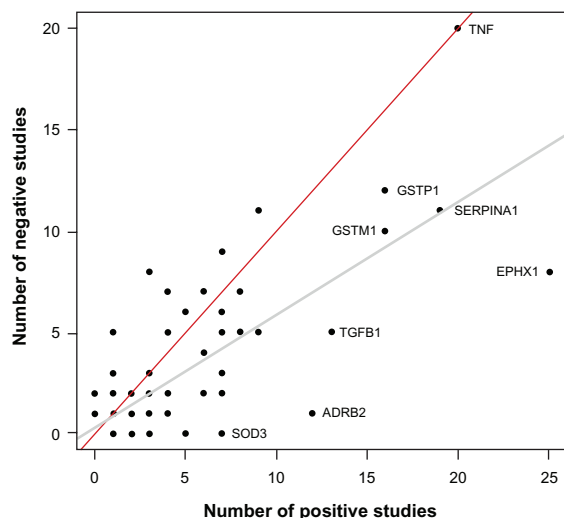
## Multi-gene-association studies

A systematic replication study of genes associated with lung function was recently conducted in the SpiroMeta Consortium.<sup>12</sup> A literature search identified 104 publications reporting a positive association with lung-function traits in the general populations of diverse origins or in cohorts of patients with respiratory diseases. A total of 130 genes and 48 intergenic regions were studied in 20,288 individuals. Among the 16,936 genotyped or imputed single-nucleotide polymorphisms (SNPs) in these loci, none was significantly associated with forced expiratory volume in one second ( $FEV_1$ ) or  $FEV_1$ /forced vital capacity (FVC) ratio after correction for multiple testing. The strongest genetic association signals with  $FEV_1$  were observed in ever-smokers in the *SERPINA1* and *PDE4D* genes.

Smaller-scale studies testing multiple genes were also conducted in China. First, 170 asthmatic cases and 347 controls were evaluated for 119 SNPs in 98 genes for association with lung function.<sup>13</sup> After correction for multiple testing, none of the SNPs was significantly associated with lung function (ie,  $FEV_1$ , FVC, or  $FEV_1$ /FVC). The strongest association was observed between rs320995 (Phe309Phe) in *CYSLTR1* and  $FEV_1$ /FVC ( $P = 0.0004$ ). Second, 1,261 SNPs in 380 candidate genes for cancer or other human diseases were tested for association with COPD in 53 cases and 107 controls with in-home coal exposure.<sup>14</sup> A total of 22 genes were associated with COPD risk, but only *PTEN* was significant after correction for multiple testing. Considering the small sample sizes, the results of these studies must be replicated before reaching firm conclusions.

## Genome-wide association studies on COPD

Table 2 summarizes COPD susceptibility loci identified by genome-wide association (GWA) studies. The results of the first GWA study on COPD were published in 2009.<sup>15</sup> The GWA study was conducted in a case-control cohort of



**Figure 2** Scatter plot showing the number of studies supporting and not supporting candidate genes for chronic obstructive pulmonary disease.

**Notes:** A total of 192 genes are illustrated. Note that many genes overlap in the lower-left corner and the 192 dots cannot be visualized on this display. The gray and red lines are the regression and identity lines, respectively. Genes studied many times or more consistently replicated are illustrated.

Norway (823 COPD cases and 810 controls), and the top 100 SNPs were followed up in the family-based International COPD Genetics Network (ICGN). Two susceptibility loci were identified. The most definitive evidence of association was found with two SNPs at the  $\alpha$ -nicotinic acetylcholine receptor locus on chromosome 15q25, the same locus implicated in the risk of lung cancer.<sup>16–18</sup> Two SNPs at the hedgehog interacting protein (HHIP) locus on chromosome 4q31 also showed strong associations.

The case-control cohort of Norway was then combined with the COPD cases from the National Emphysema Treatment Trial (NETT) and unaffected individuals from the Normative Aging Study (NAS), as well as cases and controls from the multicenter Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Study.<sup>19</sup> A total of 2940 cases and 1380 controls were considered. Loci 15q25-*CHRNA3*/*CHRNA5*/*IREB2* and 4q31-*HHIP* were replicated in this study. A third locus was also identified at 4q22.1 harboring the *FAM13A* gene. The latter was followed up and validated in the COPDGene study and the ICGN. A trend was also observed in the Boston Early-Onset COPD Study (EOCOPD). The latest GWA study on COPD was performed using 3499 cases and 1922 controls regrouping the ECLIPSE, NETT-NAS, Norway, and COPDGene studies.<sup>20</sup> The three GWA-nominated COPD-susceptibility loci (ie, *CHRNA3*/*CHRNA5*/*IREB2*, *HHIP*, and *FAM13A*) were confirmed in this extended GWA study. In addition, a new COPD locus was identified on chromosome 19q13, which

harbored the *RAB4B*, *EGLN2*, *MIA*, and *CYP2A6* genes. It was estimated that the four GWA-nominated COPD loci accounted for ~5% of the total variance of the sibling relative risk of COPD.<sup>20</sup>

Two of the four genome-wide associated loci found in COPD – 15q25 and 19q13 – were previously associated with cigarettes smoked per day and cotinine levels,<sup>21–25</sup> suggesting that the risk alleles are acting through smoking behavior. Further studies support this hypothesis on 15q25. In fact, previous studies suggested that sequence variants on chromosome 15q25 confer risk of smoking-related lung diseases (ie, COPD and lung cancer) through its effect on tobacco addiction.<sup>17,26</sup> This is consistent with the lack of association between the 15q25 locus and lung cancer among never-smokers.<sup>27–29</sup> In contrast, other evidence argues against this hypothesis, showing weak or no evidence that the 15q25 locus directly influences smoking behavior,<sup>15,16</sup> no appreciable variation in the risk of lung cancer across smoking categories,<sup>18</sup> and significant effect of the 15q25 locus on smoking-related diseases after adjustment for smoking exposure.<sup>30,31</sup> Multiple distinct loci affecting both smoking behavior<sup>24,31</sup> and lung cancer<sup>32</sup> were reported on 15q25. It is still unknown whether genes located at any of these loci are causally involved in the pathogenesis of COPD and lung cancer or the effect is mediated by changing smoking behavior. Risk alleles on chromosome 15q25 were shown to modulate the mRNA expression levels of the *CHRNA5* gene in the brain<sup>33,34</sup> and lung<sup>35</sup> tissues as well as the expression of *CHRNA5* and *IREB2* genes in sputum.<sup>36</sup> The regulation of genes in primary disease tissues, such as lung and sputum, suggests a direct effect of 15q25 genes on COPD susceptibility. More functional studies are needed to find the causal alleles and genes on 15q25 as well as to disentangle their impact on correlated traits associated with this chromosomal region.

## GWA studies on lung function

In 2007, Wilk et al<sup>37</sup> reported the first GWA study on lung function in approximately 1200 individuals. The study was conducted as part of the Framingham Heart Study. Association tests were performed on 70,987 autosomal SNPs and for ten spirometry phenotypes. No SNP was associated with lung-function phenotypes using stringent criteria for genome-wide significance, but suggestive evidence of association was provided for a nonsynonymous coding SNP in exon 5 of the *GSTO2* gene. In 2009, a larger GWA study from the Framingham Heart Study was performed in 7691 participants.<sup>38</sup> Interestingly, the 4q31-*HHIP* COPD locus

**Table 2** Susceptibility loci for chronic obstructive pulmonary disease (COPD) and related phenotypes identified by genome-wide association studies

Reference	Study*	Sample size (cases/controls)	Disease/trait	Platform (# SNPs)	Region (size)	Gene	Key SNPs
Pillai et al <sup>15</sup>	Norway <b>ICGN</b> <b>NETT-NAS</b> <b>EOCOPD</b>	823/810 <b>1891</b> <b>389/472</b> <b>949</b>	COPD	Illumina (Human Hap550)	15q25	<i>CHRNA3</i> <i>CHRNA5</i>	rs8034191 rs1051730
					4q31	<i>HHIP</i>	rs1828591 rs13118928
Cho et al <sup>19</sup>	Norway NETT-NAS ECLIPSE <b>COPDGene</b> <b>EOCOPD</b> <b>ICGN</b>	2940/1380  <b>502/504</b> <b>949</b> <b>2859</b>	COPD	Illumina (Human Hap550 or Quad610)	4q22	<i>FAM13A</i>	rs7671167 rs1903003
					15q25	<i>CHRNA3</i> <i>CHRNA5</i> <i>IREB2</i>	rs1062980
					4q31	<i>HHIP</i>	rs1828591
Cho et al <sup>20</sup>	ECLIPSE NAS-NETT GenKOLS COPDGene <b>ICGN</b>	1764/178 373/435 863/808 499/501 <b>983 probands/ 1876 siblings</b>	COPD	Illumina (Human Hap550, Quad610, or Omni1 Quad)	19q13	<i>RAB4B</i> <i>EGLN2</i> <i>MIA</i> <i>CYP2A6</i>	rs7937 rs2604894
					4q22	<i>FAM13A</i>	rs1964516 rs7671167
					4q31	<i>HHIP</i>	rs13141641 rs13118928
					15q25	<i>CHRNA3</i> <i>CHRNA5</i> <i>IREB2</i>	rs11858836 rs13180
					10q25	<i>GSTO2</i>	rs156697
Wilk et al <sup>37</sup>	FHS	1059–1222	Ten spirometry phenotypes	Affymetrix (70,987)	10q25	<i>GSTO2</i>	rs156697
Wilk et al <sup>38</sup>	FHS <b>Family heart study</b>	7691 <b>835</b>	FEV <sub>1</sub> /FVC	Affymetrix (500 K + 50 K)	4q31	<i>HHIP</i>	rs13147758
Repapi et al <sup>40</sup>	SpiroMeta Consortium <b>CHARGE consortium</b> <b>Health 2000 survey</b>	20,288 <b>32,184</b> <b>21,209</b> <b>883</b>	FEV <sub>1</sub> and FEV <sub>1</sub> /FVC	Affymetrix and Illumina (2.5 million)	4q31	<i>HHIP</i>	rs12504628
					2q35	<i>TNS1</i>	rs2571445
					4q24	<i>GSTCD</i>	rs10516526
					5q33	<i>HTR4</i>	rs3995090
					6p21	<i>AGER</i>	rs2070600
Hancock et al <sup>39</sup>	<b>CHARGE Consortium SpiroMeta consortium</b>	20,890 <b>16,178</b>	FEV <sub>1</sub> /FVC	Affymetrix and Illumina (2,515,866)	15q23	<i>THSD4</i>	rs12899618
					2q36	<i>PID1</i>	rs1435867
					4q22	<i>FAM13A</i>	rs2869967
					4q31	<i>HHIP</i>	rs1980057
					5q33	<i>HTR4</i>	rs11168048
					5q33	<i>ADAM19</i>	rs2277027
					6p21	<i>AGER-PPT2</i>	rs2070600
6q24	<i>GPR126</i>	rs3817928					

(Continued)

Table 2 (Continued)

Reference	Study*	Sample size (cases/controls)	Disease/trait	Platform (# SNPs)	Region (size)	Gene	Key SNPs
			FEV <sub>1</sub>		9q22 4q24	<i>PTCH1</i> <i>INTS12</i> <i>GSTCD</i> <i>NPNT</i>	rs16909898 rs17331332
Soler Artigas et al <sup>41,**</sup>	23 studies <b>17 studies</b>	48,201 <b>46,411</b>	FEV <sub>1</sub>	Illumina and Affymetrix (2,706,349)	3q26	<i>MECOM</i>	rs134555
			FEV <sub>1</sub> /FVC		6p22 10q22 1p36 1q41 2q37 3p24 5q15 6q21 6p21 12q13 12q22 16q13 16q23 21q22	<i>ZKSCAN3</i> <i>C10orf11</i> <i>MFAP2</i> <i>TGFB2</i> <i>LYPLAL1</i> <i>HDAC4</i> <i>FLJ43879</i> <i>RARB</i> <i>SPATA9</i> <i>RHOBTB3</i> <i>ARMC2</i> <i>NCR3-AIF1</i> <i>LRP1</i> <i>CCDC38</i> <i>MMP15</i> <i>CFDP1</i> <i>KCNE2</i> <i>LINC00310</i>	rs6903823 rs11001819 rs2284746 rs993925 rs12477314 rs1529672 rs153916 rs2798641 rs2857595 rs11172113 rs1036429 rs12447804 rs2865531 rs9978142
Imboden et al <sup>42</sup>	SAPALDIA ECRHS EGEA <b>FHS</b> <b>ARIC</b> <b>B58C</b> <b>Dutch</b> <b>asthma</b> <b>study</b>	2677 nonasthmatic, 1441 asthmatic  <b>10,858 nonasthmatic,</b> <b>1138 asthmatic</b>	FEV <sub>1</sub> and FEV <sub>1</sub> /FVC FEV <sub>1</sub> decline in nonasthmatic	Illumina Human 610quad	10p23 13q14	<i>CDC123</i> <i>DLEU7</i>	rs7068966 rs9316500
			FEV <sub>1</sub> /FVC decline in asthmatic		8p22	<i>TUSC3</i>	rs4831760
Kong et al <sup>43</sup>	ECLIPSE Norway	1557 432	Emphysema (qualitative)	Illumina Human Hap550 (499,578)	12q11	<i>BICD1</i>	rs10844154 rs161976
Wan et al <sup>44</sup>	ECLIPSE Norway NETT <b>COPDGene</b>	1734 851 365 <b>502</b>	Cachexia-related phenotypes (BMI and fat-free mass index)	Illumina	16q12	<i>FTO</i>	rs8050136

**Notes:** \*Bold entries indicates replication cohorts; \*\*only the new loci are identified for this study, but ten loci previously reported by Hancock et al<sup>39</sup> and Repapi et al<sup>40</sup> were also detected.

**Abbreviations:** ARIC, Atherosclerosis Risk in Communities; B58C, British 1958 Birth Cohort; EOCOPD, Boston Early-Onset COPD Study; BMI, body mass index; COPDGene, COPDGene study; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; ECRHS, European Community Respiratory Health Survey; EGEA, Epidemiological study on the Genetics and Environment of Asthma; FEV<sub>1</sub>, forced expiratory volume in 1 second; FHS, Framingham Heart Study; FVC, forced vital capacity; GenKOLS, Bergen, Norway COPD Cohort; ICGN, International COPD Genetics Network study; NAS-NETT, Normative Aging Study and National Emphysema Treatment Trial; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults; SNPs, single-nucleotide polymorphisms.

was associated with percent predicted FEV<sub>1</sub>/FVC ratio. This locus was confirmed in a second set of participants from the Family Heart Study (n = 835).

In January 2010, two articles reported GWA studies for lung function.<sup>39,40</sup> First, Repapi et al<sup>40</sup> performed a GWA

study on FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio in the SpiroMeta consortium (20,288 individuals of European ancestry). They have also followed up the best associated SNPs in 32,184 additional individuals. Overall, they have identified five novel genome-wide significant loci for pulmonary function,

being 2q35 (*TNSI*), 4q24 (*GSTCD*), and 5q33 (*HTR4*) for FEV<sub>1</sub>, and 6p21 (*AGER*) and 15q23 (*THSD4*) for FEV<sub>1</sub>/FVC. Second, Hancock et al<sup>39</sup> conducted a GWA study on the same two clinically important pulmonary function measures in the CHARGE consortium consisting of 20,890 participants of European ancestry. They identified significant associations with FEV<sub>1</sub>/FVC ratio for SNPs located in seven previously unrecognized loci: 6q24 (*GPR126*), 5q33 (*ADAM19*), 6p21 (*AGER* and *PPT2*), 4q22 (*FAM13A*), 9q22 (*PTCH1*), 2q36 (*PIDI*), and 5q33 (*HTR4*). For FEV<sub>1</sub>, one new locus annotated by three genes (*INTS12*, *GSTCD*, and *NPNT*) on 4q24 was identified. 4q24 (*GSTCD*), 5q33 (*HTR4*) and 6p21 (*AGER*) were common in both consortia, ie, SpiroMeta and CHARGE. The previously reported 4q31 locus located upstream of the *HHIP* gene associated with FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio was also confirmed in these consortia.

More recently, a larger GWA study of FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio was reported, comprising more than 48,000 individuals of European ancestry and followed up for replication in more than 46,000 individuals.<sup>41</sup> Ten out of eleven loci previously reported by the SpiroMeta and CHARGE consortia were replicated in this extended GWA study. Only *PIDI* on 2q36 was not replicated. More interestingly, 16 new loci were identified, including twelve loci for FEV<sub>1</sub>/FVC, three for FEV<sub>1</sub>, and one for both traits. Thus, 26 loci were associated with lung function in this GWA study. Together, these loci explain 3.2% of the additive polygenic variance for FEV<sub>1</sub>/FVC and 1.5% of the variance for FEV<sub>1</sub>.

The first GWA study on lung-function decline was recently reported.<sup>42</sup> Briefly, genome-wide analyses on FEV<sub>1</sub> and FEV<sub>1</sub>/FVC decline were conducted in 2677 nonasthmatics and 1441 asthmatics separately. The top hits were then replicated in 10,858 nonasthmatic and 1138 asthmatic participants. Decline of FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio was evaluated during a follow-up examination period of roughly 10 years in these participants. No SNP reached genome-wide significance in the discovery set. However, one locus on chromosome 13q14.3 containing the *DLEU7* gene was strongly associated with FEV<sub>1</sub> decline in nonasthmatics from the discovery set and confirmed in the replication set. A strong association signal was also reported on 8p22 harboring the *TUSC3* gene for FEV<sub>1</sub>/FVC decrease in asthmatics, but not validated in the replication set. Many loci previously associated with cross-sectional lung function in GWA studies described above were replicated with baseline lung function in either asthmatic or nonasthmatic subjects. However, few GWAS-nominated lung-function loci were associated with lung-function decline, suggesting different

genetic mechanisms governing baseline lung function and decline with age. In addition, this study showed the genetic heterogeneity of lung-function decline between subjects with and without asthma. Table 2 summarizes lung-function susceptibility loci identified by GWA studies.

## GWA studies on COPD-related phenotypes

Other GWA studies were reported on COPD-related phenotypes. Emphysema is an important feature of COPD and varies considerably between patients. A recent GWA study was performed on emphysema measures by computed tomography scan and defined by radiologist qualitative scores and quantitative assessments of low-attenuation areas.<sup>43</sup> The qualitative scores obtained in 1557 patients from the ECLIPSE study and 432 subjects from the Norway cohort led to the identification of an emphysema locus on chromosome 12p11.2. The most strongly associated SNP is located in the *BICD1* gene, known to be involved in regulating telomere length. The ECLIPSE, Norway, and NETT studies were also used to perform a GWA study on COPD-related cachexia phenotypes, including body mass index and fat-free mass index.<sup>44</sup> Cachexia occurs in approximately 10% of patients with COPD and is associated with increased mortality. The GWA study on body mass index and fat-free mass index in patients with COPD identified a single susceptibility locus that harbored the *FTO* gene, the most robust gene associated with obesity. Whether *FTO* acts through obesity or directly affects lung function remains to be elucidated.

GWA studies on COPD, lung function, and related phenotypes provided strong and consistent evidence of genetic susceptibility loci. These studies also highlight the large number of participants required to identify reproducible genetic loci. So far, GWA studies have identified only a small fraction of the genetic variants contributing to COPD risk, related complications, and lung-function variability. GWA studies on larger sample sizes, especially for COPD, will be required to identify the genetic factors underpinning COPD and related phenotypes. Large international efforts are under way to increase sample sizes and use more comprehensive molecular phenotyping (eg, gene expression in the lung) to elucidate the genetic component of COPD.<sup>45,46</sup> It should be emphasized that the causal genes and genetic variants of all these newly discovered loci by GWA studies remain to be identified. More integrative genomic approaches will be required for these purposes. Different study designs testing rare and copy-number variants as well as gene-smoking interaction are also needed.

## Integrative genomic approaches

More studies are being conducted using integrative genomic approaches in order to identify COPD susceptibility genes. For example, the *IREB2* gene was identified by combining gene expression in human lungs and genetic association in COPD cohorts.<sup>47</sup> In this study, lung specimens were obtained from patients undergoing lung nodule resection, and gene expression was compared between 15 COPD and 18 non-COPD patients using whole-genome gene-expression arrays. A total of 889 SNPs found in the 62 genomic regions containing genes differentially expressed between patients with or without COPD were tested for association with COPD and lung function. Seventy-one SNPs nominally associated ( $P \leq 0.05$ ) with COPD in the NETT-NAS study were followed up for replication in the EOCOPD study. A gene-based replication was then completed to confirm genetic association between genetic variants in the *IREB2* gene and lung function. Overall, the *IREB2* gene was shown to be upregulated in lung specimens of COPD patients and to contain genetic variants associated with COPD. Gene expression in a larger number of lung specimens will be required to test whether COPD-associated SNPs in the *IREB2* gene influence the expression of its gene product.

Although Table 2 shows the major susceptibility loci identified by GWA studies, many additional loci were borderline significant in these studies. Many true positives are likely to be missed by this approach owing to the stringent threshold used to control for false-discovery rates. Different weighting methods and SNP-prioritization strategies are currently used to find true-positive signals from previous GWA studies. For example, the *FGF7* gene was recently identified as a COPD susceptibility locus by weighting GWA analysis on regions of conserved homozygosity haplotype in subjects affected with COPD compared to unaffected subjects.<sup>48</sup> As mentioned previously,<sup>49</sup> further studies reanalyzing genome-wide SNP datasets with weighting methods based on function annotations (eg, coding variants or regions) or prior knowledge (eg, candidate genes or genome-wide linkage studies) will be required. Similarly, ongoing lung expression quantitative trait loci (eQTLs) mapping data<sup>36,46</sup> are likely to leverage the impact of previous GWA studies on COPD by providing a list of SNPs that regulate gene expression in relevant tissues. SNPs associated with gene expression will provide crucial functional information to understand the molecular changes introduced by the susceptibility DNA variants. The identification of SNPs associated with both disease traits and quantitative transcript

levels of one or more genes in relevant tissues will highlight the most likely causal gene within the susceptibility loci and the functional SNPs that are prime candidates to be directly involved in the pathogenesis of COPD.

## Conclusion

Elucidating the genetic component of COPD and lung function turned out to be a challenging task. Major resources and collaborative efforts will be required to achieve our goal. In this review, the author provides an updated list of COPD genes and a summary of GWAS results conducted during the last few years. It is hoped that the gene list can be used by investigators to replicate or refute susceptibility genes of COPD. As eluded above, this gene list can also be used to reanalyze GWA data by prioritizing genes previously associated with COPD or related phenotypes or enter into more global gene network and causality analyses. Owing to the challenge faced by the genetic community, large collections of patients well characterized for COPD phenotypes are ongoing to identify the genuine COPD genes. A lumping and splitting strategy is an old idea in the field of genetics of complex traits<sup>50</sup> that will certainly be essential in the field of COPD. Pooling resources (ie, lumping) is required to obtain proper sample sizes, but is likely to increase heterogeneity. These larger sample sizes, however, provide the opportunity to subdivide (ie, splitting) the pooled data into more homogeneous subgroups where the molecular defects are more likely to be similar. Accordingly, not only the genetic community but the entire spectrum of experts managing and treating patients with COPD will be required to provide samples, precise phenotypes, and expertise to search for the underlying genetic mechanisms. In parallel, complementary multidimensional genomic data in relevant tissues (eg, lung eQTLs) will be crucial to uncover causal genes and genetic variants that contribute to COPD and to discover new molecular targets for prevention, diagnosis, and treatment.

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## Disclosure

The author reports no conflict of interest in this work.

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## Supplementary materials

**Table S1** Genes tested but showing lack of association with chronic obstructive pulmonary disease

Symbol	Name	Chromosome	References			
			Single studies		Meta-analyses	
			Positive	Negative	Positive	Negative
<i>AGER</i>	Advanced glycosylation end product-specific receptor	6		1,2		
<i>CASP8</i>	Caspase 8, apoptosis-related cysteine peptidase	2		3		
<i>CCL17 (TARC)</i>	Chemokine (C-C motif) ligand 17	16		4		
<i>CCL2</i>	Chemokine (C-C motif) ligand 2	17		5		
<i>CFLAR</i>	CASP8 and FADD-like apoptosis regulator	2		3		
<i>COL6A5</i>	Collagen, type VI, alpha 5	3		6		
<i>CXADR</i>	Coxsackie virus and adenovirus receptor	21		7		
<i>CYP1B1</i>	Cytochrome P450, family 1, subfamily B, polypeptide 1	2		8,9		
<i>CYP2D6</i>	Cytochrome P450, family 2, subfamily D, polypeptide 6	22		10		
<i>DCN</i>	Decorin	12		11		
<i>DNAJB1</i>	Dnaj (Hsp40) homolog, subfamily B, member 1	19		12		
<i>EDNRA</i>	Endothelin receptor type A	4		13		
<i>FGA</i>	Fibrinogen alpha chain	4		14		
<i>FGB</i>	Fibrinogen beta chain	4		14,15		
<i>FGG</i>	Fibrinogen gamma chain	4		14		
<i>FKBP4</i>	FK506 binding protein 4, 59 kDa	12		12		
<i>FKBP5</i>	FK506 binding protein 5	6		12		
<i>FLCN</i>	Folliculin	17		16		
<i>GABPA</i>	GA binding protein transcription factor, alpha subunit 60 kDa	21		17		
<i>GPX1</i>	Glutathione peroxidase 1	3		18,19		
<i>GSTM3</i>	Glutathione S-transferase mu 3 (brain)	1		20		
<i>HDAC2</i>	Histone deacetylase 2	6		1		
<i>HDAC5</i>	Histone deacetylase 5	17		1		
<i>HSP90AA1 (HSPCA)</i>	Heat shock protein 90 kDa alpha (cytosolic), class A member 1	14		12		
<i>HSP90AB1 (HSPCB)</i>	Heat shock protein 90 kDa alpha (cytosolic), class B member 1	6		12		
<i>HSPA1A</i>	Heat shock 70 kDa protein 1A	6		21		
<i>HSPA1B</i>	Heat shock 70 kDa protein 1B	6		21		
<i>HSPA1L</i>	Heat shock 70 kDa protein 1-like	6		21		
<i>HSPA8</i>	Heat shock 70 kDa protein 8	11		12		
<i>IL11</i>	Interleukin 11	19		1		
<i>IL13RA2</i>	Interleukin 13 receptor, alpha 2	X		22		
<i>ITGB5</i>	Integrin, beta 5	3		7		
<i>JAK3</i>	Janus kinase 3	19		1		
<i>KCND2</i>	Potassium voltage-gated channel, Shal-related subfamily, member 2	7		1		
<i>MAP3K5</i>	Mitogen-activated protein kinase kinase kinase 5	6		1		
<i>MIR146a</i>	MicroRNA 146a	5		23		
<i>MRPL44</i>	Mitochondrial ribosomal protein L44	2		24		
<i>ORMDL3</i>	ORM1-like 3 ( <i>S cerevisiae</i> )	17		25		
<i>PTGES3</i>	Prostaglandin E synthase 3 (cytosolic)	12		12		
<i>RARRES2</i>	Retinoic acid receptor responder (tazarotene induced) 2	7		1		
<i>SCGB1A1 (CC16)</i>	Secretoglobulin, family 1A, member 1 (uteroglobin)	11		26		
<i>SOD1</i>	Superoxide dismutase 1, soluble	21		18,27		
<i>TBX21</i>	T-box 21	17		28		
<i>THSD4</i>	Thrombospondin, type 1, domain containing 4	15		2		
<i>TLR2</i>	Toll-like receptor 2	4		29,30		
<i>TLR6</i>	Toll-like receptor 6	4		31		
<i>TNFRSF1A</i>	Tumor necrosis factor receptor superfamily, member 1A	12		32		
<i>TNFRSF1B</i>	Tumor necrosis factor receptor superfamily, member 1B	1		32		

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