Published in final edited form as:
Med Clin North Am. 2012 July ; 96(4): 699–711. doi:10.1016/j.mcna.2012.02.006.

Genes and COPD

Marilyn Foreman, M.D., M.S.[1,*], **Michael Campos, M.D.**[2,*], and **Juan C. Celedón, M.D., Dr.P.H.**[3,4,**]

[1]Division of Pulmonary and Critical Care Medicine, Dept. of Medicine, Morehouse School of Medicine

[2]Division of Pulmonary, Critical Care and Sleep Medicine, Dept. of Medicine, University of Miami Miller School of Medicine

[3]Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Dept. of Pediatrics, Children's Hospital of Pittsburgh of UPMC

Division of Pulmonary, Allergy and Critical Care Medicine, Dept. of Medicine, University of Pittsburgh School of Medicine

SYNOPSIS

The marked variability in individual susceptibility to the detrimental effects of smoking on lung function and findings suggest a significant genetic contribution to COPD, which has been demonstrated in several studies. The only known genetic risk factor for COPD, severe alpha 1 antitrypsin (AAT) deficiency, explains only 1–2% of cases of this disease. Screening for severe AAT should be conducted in all cases of COPD. Intravenous augmentation therapy should be combined with currently recommended treatment modalities for COPD when treating patients with COPD due to severe AAT deficiency. There is considerable interest in identifying susceptibility genes for COPD unrelated to severe AAT deficiency, as this could greatly enhance current efforts to prevent, diagnose and treat this disease by yielding novel insights into its pathogenesis. Genome-wide association studies (GWAS) of COPD and its intermediate phenotypes (e.g., lung function measures) have identified novel susceptibility loci for COPD. Some of these susceptibility loci may also influence lung function in the general population (e.g., *HHIP* and *FAM13A*), while others may affect not only COPD but other diseases related to smoking behavior (e.g., *CHRNA3/CHRNA5*). Although much work remains to be done, recent advances and the implementation of novel approaches to study COPD genetics (e.g., sequencing) and epigenetics are promising, and could have a profound impact on COPD management.

**Corresponding author: Juan C. Celedón, M.D., Dr.P.H., F.A.C.P., F.C.C.P., Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Avenue, Pittsburgh, PA 15224, Phone: 412.692.8429; Fax: 412.692.7636, juan.celedon@chp.edu.
*These authors contributed equally to this manuscript
***Contact Information: Marilyn Foreman, M.D., M.S., Division of Pulmonary and Critical Care Medicine, Dept. of Medicine, Morehouse School of Medicine, 720 Westview Drive SW, Atlanta, GA 30310-1495, Phone: (404) 616-4658; Fax: (404) 616-5474, mforeman@msm.edu
Michael Campos, M.D., Division of Pulmonary, Critical Care and Sleep Medicine (R-47), University of Miami Miller School of Medicine, 1600 N.W. 10th Ave., RMSB 7052, Miami, FL 33136, Phone: (305) 243-3045; Fax: (305) 243-6992, mcampos1@med.miami.edu

Keywords

COPD; genetics; alpha 1 antitrypsin deficiency

INTRODUCTION

Severe alpha 1-antitrypsin (AAT) deficiency is the only well-established genetic risk factor for chronic obstructive pulmonary disease (COPD). Patients with severe AAT deficiency (most commonly, Protease Inhibitor [PI] Z) are at increased risk for developing COPD, particularly if they smoke[1–2]. However, severe AAT deficiency explains only a small proportion of cases of COPD (1–2%), and genes other than PI type (genetic modifiers) likely influence lung function in PI Z subjects[3–4].

Burrows et al. noted that the development of chronic airflow obstruction in response to cigarette smoking is highly variable in the general population, suggesting that individuals vary in their genetic susceptibility to the detrimental effects of smoking on lung function[5]. Several studies have since confirmed a genetic contribution to the pathogenesis of COPD in cigarette smokers without severe AAT deficiency[6–8]. A search for COPD-susceptibility genes other than PI type has included genome-wide linkage analyses, candidate-gene studies and, more recently, genome-wide association studies (GWAS).

In this chapter, we review the genetics, diagnosis and treatment of severe AAT deficiency. We then assess findings from recent genetic studies of COPD and its intermediate phenotypes (e.g., lung function). Finally, we briefly discuss future directions in this field.

COPD DUE TO SEVERE AAT DEFICIENCY

Severe deficiency of AAT was first recognized as a risk factor for COPD in 1963[9]. Since then, many studies have characterized the genetics and role of this protein in the pathogenesis of COPD.

Genetics

The AAT protein is encoded by a 12.2 kb gene located on chromosome 14q32.1 called *SERPINA1* or *PI*[10]. The gene has seven exons and six introns, is inherited in an autosomal codominant fashion, and has more than 120 single nucleotide polymorphisms (SNPs)[11]. Numerous AAT protein variants can be differentiated by their speed of migration on gel electrophoresis using isoelectric focusing. The most common alleles are M, S and Z. The M variants (M1, M2, M3) result in proteins with a medium rate of migration and a normal level of AAT, the S variant is associated with mild reductions in serum AAT level, and the Z variant has the slowest rate of migration and leads to severe reduction of AAT level. Null alleles also occur, with undetectable protein levels. Combinations of the M, S and Z variants are seen in >95% of the population. Serum AAT levels in subjects with the MZ and ZZ phenotypes are 60% and 10%, respectively, of those in (normal) subjects with the MM phenotype.

The most common forms of severe AAT deficiency with a high risk of COPD involve combinations of two Z alleles (Glu342Lys) and a Z allele with a null allele (both referred as phenotype PI*Z), or a combination of two null alleles. Combinations of a Z allele and an S allele (Glu264Val) also confer a moderate risk of COPD[12]. The phenotype MZ has also been associated with a lower but still increased risk of COPD, while the MS phenotype has been associated with only mild reductions in AAT level and no risk of COPD[13]. AAT deficiency has been described in all races, although the highest frequencies of the Z allele

have been described in whites. In the United States, the frequency of the ZZ phenotype is 1 in 4775, SZ phenotype 1 in 1124 and MZ phenotype 1 in 36 individuals[14]. Worldwide, severe AAT deficiency affects approximately 3.4 million individuals[15].

Pathophysiology

SERPINA1 codes a 52 kDa glycoprotein with 394 amino acids that contains a reactive loop with an active site at methionine 358. Although AAT is an acute phase reactant synthesized mostly by liver cells, there also is local synthesis by cells such as neutrophils, monocytes, macrophages and epithelial cells[16–17]. The major function of AAT is the neutralization of serine proteases, particularly neutrophil elastase (NE); other targets include cathepsin G, trypsin and proteinase-3[18–19]. Severe deficiency of AAT results in excess protease activity in the lungs, particularly during periods of inflammation, and leads to progressive degradation of the lung parenchyma (emphysema) and accelerated decline in lung function over time[20]. Although protease-antiprotease imbalance is the most important cause of COPD in severe AAT deficiency, the loss of other functions of AAT likely contribute in COPD pathogenesis. These include endothelial cell protection against apoptosis by binding to caspases[21], regulation of airway epithelial lining fluid balance by binding to matryptase[22], and inflammatory response modulation. For example, AAT modulates endotoxin-induced inflammation[23], reduces TNF-alpha-induced lung injury in rabbits[24], inhibits superoxide production by neutrophils[25] and regulates the response of macrophages to pro-inflammatory stimuli[26].

Z-AAT has reduced capacity to inhibit NE[27], as well as a conformational protein change that enables a loop-sheet polymerization process and its accumulation in the endoplasmic reticulum (ER) with loss of secretion into the circulation[28]. The Z-polymers are degraded by ER-associated degradation pathways via proteasomes and by autophagy as part of the ER overload response[29]. If these cellular mechanisms fail, gain-of-toxic function and ER stress occur, which can lead to inflammation via NFkB activation[30], hepatocyte death by apoptosis[31] and –ultimately- liver disease, both during childhood and later in life; a similar process may occur in the lung but has not been as well characterized.

AAT polymers can also further worsen protease-antiprotease imbalance. When instilled in the trachea of mice, Z-polymers produce a significant concentration dependent influx of neutrophils that is not mediated by chemokines[32]. The polymers can be detected in the circulation[33] and in bronchoalveolar lavage fluid of patients with severe AAT deficiency, in whom they may also induce inflammation by a direct effect on epithelial cells[34].

Diagnosis

Compared to young subjects who have a PI*ZZ phenotype but do not smoke, those who have a PI*ZZ phenotype and do smoke have significantly lower FEV_1/FVC and diffusing capacity of carbon monoxide[35]. At age 30 years, Pi*Z subjects who smoke have significantly more shortness of breath, sputum production and wheezing than Pi*MM smokers; among nonsmokers, Pi*ZZ subjects report only more wheezing than non-affected controls[35].

Not uncommonly, clinicians stereotype the presentation of severe AAT deficiency as that of a young (<40 years old) white non-smoker who presents with COPD and pan-acinar emphysema predominantly in the lower lobes. Although some affected individuals present this way, most symptomatic individuals have features that resemble those of COPD not due to severe AAT deficiency. About a third of affected subjects have a more indolent presentation and are diagnosed after age 50 years[36], about a third have emphysema predominantly located in the upper lobes[37] and more than 80% have a significant smoking

history[38]; bronchiectasis of variable severity are also common[39]. Current guidelines thus recommend screening for severe AAT deficiency in all patients with COPD[40]. Screening of relatives of affected subjects may find nonsmokers with the PI*ZZ phenotype but no respiratory symptoms[41].

Genetic Modifiers

The significant variability observed in the development, progression and manifestations of COPD due to severe AAT deficiency strongly suggests that genetic and/or environmental factors modify disease expression. Studies of familial aggregation and heritability suggest that genetic factors other than PI type influence lung function and airflow obstruction in PI*Z individuals[3, 42]. Although no genetic modifiers of severe AAT deficiency have been confidently identified, candidate genes have been examined. In a case-control study, two coding polymorphisms in NOS3 were associated with severe airflow obstruction in PI*Z individuals[43]. In a family-based association study of 10 genes previously associated with asthma and/or COPD, variants in the genes for TNF and IL10 were associated with lung function measures[44].

In subjects with severe AAT deficiency, the development of airflow obstruction is associated with age, male sex, bronchodilator responsiveness and chronic bronchitis, and - most strongly- cigarette smoke[45–47].

Treatment

A detailed description of how to treat lung disease in severe AAT deficiency is beyond the scope of this chapter. The pharmacologic and non-pharmacologic treatment of COPD due to AATD follows the same guidelines as those for COPD in general[48] Interventions showing benefit in subjects with severe AAT deficiency include disease management programs (which improve quality of life and decrease healthcare utilization[49]), lung volume reduction surgery (which improve 6-minute walking test and dyspnea scores[50]) and inhaled steroids (which reduce airflow obstruction and hyperinflation[51].

Intravenous augmentation therapy with donor-derived purified AAT is the only FDA-approved specific treatment for lung disease due to severe AAT deficiency (defined as a baseline serum AAT level below 11 μM)[40]. The recommended dose (60 mg/kg once a week) is intended to keep trough serum AAT above 11 μM. Studies supporting this therapy are mostly observational[52]. Whereas results from a recent meta-analysis of observational studies suggest that augmentation therapy with AAT slows lung function decline in subjects with moderately reduced lung function[53], a meta-analysis of the only two published randomized placebo-controlled trials concluded that there was not sufficient evidence to recommend this therapy[54]. In spite of this controversy, augmentation therapy should be used while the effectiveness, optimal dosage, therapeutic goals and target populations for this treatment are further studied. Additional potential treatments for severe AAT deficiency are being examined, including gene therapy[55] and correction of the underlying genetic defect using inducible stem cells[56].

GENETICS OF COPD UNRELATED TO SEVERE AAT DEFICIENCY

Findings from studies of candidate genes for COPD susceptibility, reviewed in detail elsewhere[57], have yielded additional insight into our understanding of COPD pathobiology, particularly for certain pathways (e.g., TGF-beta, matrix metalloproteinases)[57–58]. In contrast to studies of one or few genes selected on the basis of known biology, GWAS are hypothesis-free studies that leverage information from markers genotyped along the entire genome, and can thus yield unanticipated discoveries and insights into disease pathogenesis.

Findings from recent GWAS and other new approaches to study COPD genetics are the focus of this review.

GWAS of COPD

Published GWAS of COPD are summarized in Table 1. In 2009, Pillai and colleagues performed the first GWAS of COPD using a multi-stage replication design[59]. The discovery (primary or initial) cohort comprised 823 subjects with COPD (cases) and 810 unaffected smokers (controls) from Bergen, Norway. The 100 SNPs with the lowest P values in the GWAS of this cohort were then tested for association with COPD in 1,891 members of 606 white families from the family-based International COPD Genetics Network (ICGN). Seven of the 100 SNPs tested in ICGN showed significant evidence of association and were then tested for association with COPD in 389 cases from the National Emphysema Treatment Trial (NETT) and 472 smoking controls from the Normative Aging Study (NAS). Six of these seven SNPs were also tested for association with lung function measures in 949 members of 127 families in the Boston Early-Onset COPD Study (BEOCOPD)[60]. Two SNPs (rs8034191 and rs1051730) in the α-nicotinic acetylcholine receptor (*CHRNA3/CHRNA5/IREB2*) locus on chromosome (chr.) 15 showed significant evidence of association with COPD susceptibility in ICGN and NETT-NAS, and reached genome-wide (GW) statistical significance in the analysis of three combined cohorts (Norway, ICGN and NETT-NAS) but were not GW significant in the discovery cohort. Nominal evidence of significant associations with FEV_1 was also noted in BEOCOPD (P=0.03 for each polymorphism) and ICGN ($P= 1.04 \times 10^{-4}$ for rs8034191 and 1.75×10^{-5} for rs1051730). Polymorphisms in the gene for hedgehog interacting protein (*HHIP*) on chromosome 4 were consistently replicated but did not reach GW statistical significance in the discovery cohort or the combined analysis. The hedgehog signaling pathway has received continued attention (see below) due to its involvement in branching morphogenesis of the lung[61].

Family with sequence similarity 13, member A (*FAM13A*) was identified as a susceptibility gene for COPD in a GWAS of a cohort comprising 4,320 subjects enrolled in three case-control studies: Norway, NETT- NAS, and the multicenter Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE[62])[63]. Replication was then attempted in 502 cases and 504 controls from COPDGene (a multicenter study of the genetics and epidemiology of COPD)[64], BEOCOPD, and ICGN. A polymorphism in *FAM13A* (rs7671167) on chr. 4q22.1 was associated with COPD in the discovery cohort and in two of the three replication cohorts (combined P value= 1.2×10^{-11}, combined odds ratio (OR) in the case-control studies=0.76, 95% confidence interval [CI]=0.69–0.83). This SNP was also associated with pre-bronchodilator FEV_1 in BEOCOPD (P = 0.02) and with pre- ($P=5.3 \times 10^{-5}$) and post-bronchodilator FEV_1 in ICGN.

Intermediate phenotypes offer several advantages for genetic studies of complex diseases such as COPD because they are objectively defined and may be influenced by fewer genes than the disease *per se*. Kong et al. conducted a meta-analysis of GWAS results from the Norway, ECLIPSE and NETT cohorts on percent emphysema from computed tomography (defined by densitometry as the percentage of lung voxels at −950 Hounsfield Units, and also qualitatively by visual scoring)[65]. Though no SNPs in any of the three cohorts were significantly associated with emphysema, a SNP (rs10844154) in the gene for bicaudal homolog 1 (*BICD1*) on chr. 12 reached GW significance for association in the meta-analysis of emphysema (OR for at least mild emphysema=1.46, $P= 5.2 \times 10^{-7}$ and OR for at least moderate emphysema=1.56, $P=4.8 \times 10^{-8}$) in computed tomography (CT). Interestingly, the strongest signal in this study came from radiologist scoring rather than density mask analysis though the authors stressed that this did not imply superiority of one method over the other. The authors noted that variants in *BICD1* are associated with length of telomeres, suggesting

that a mechanism linked to accelerated aging may be involved in the pathogenesis of emphysema.

Five SNPs in loci previously associated with COPD (*HHIP*, *CHRNA3/CHRNA5/IREB2*, and *FAM13A*), were tested for association with COPD-related phenotypes (smoking behavior, lung function, body mass index [BMI], fat-free body mass, BODE index[66], emphysema and airway wall thickness determined by CT) in ECLIPSE and then validated in ICGN[67]. A SNP in the *CHRNA*3/*CHRNA*5 locus (rs8034191) was associated with increased smoking intensity (expressed as pack-years), radiologist's assessment of emphysema on high-resolution CT of the chest, and airflow obstruction in the ECLIPSE and ICGN cohorts. In ECLIPSE, subjects with COPD who were current or former smokers and homozygous for the rs8034191 risk allele had 7.5 more cumulative pack-years of smoking (P=0.002) than those who were heterozygous or homozygous for the non-risk allele; this association was confirmed in the ICGN. SNPs in *HHIP* or *FAM13A* loci were not associated with smoking intensity. A SNP in *HHIP* was associated with FEV_1/FVC in the ECLIPSE and ICGN cohorts; this SNP was also significantly associated with fat-free body mass and COPD exacerbations in ECLIPSE. *FAM13A* SNPs were associated with lung function but this association was not consistently significant across cohorts. These findings, taken together with others, suggest that: 1) the *CHRNA3/CHRNA5* locus, which has also been associated lung cancer[68], influences COPD-related phenotypes –at least partly-through its effects on smoking behavior[69]; 2) the *HHIP* locus, which has also been associated with lung cancer[70] and lung function in subjects with asthma[71], has effects on lung function and the systemic component(s) of COPD; and 3) *FAM13A* influences lung function and airflow obstruction.

Cachexia, which is common in subjects with advanced COPD, is associated with increased severity of airflow obstruction and increased mortality. Wan et al. conducted a GWAS of BMI in 2,950 subjects with COPD in three cohorts (ECLIPSE, Norway and NETT), with replication attempted in 502 subjects from COPDGene[72]. A GWAS of fat-free mass index (FFMI) was also conducted in the ECLIPSE and Norway cohorts. SNP rs8050136, located in the intron of the fat mass and obesity–associated gene (*FTO*) was significantly associated with BMI ($P=4.97 \times 10^{-7}$) and FFMI ($p = 1.19 \times 10^{-7}$) in the discovery cohort. Findings for BMI were replicated in COPDGene ($P=6 \times 10^{-3}$). These findings suggest that *FMO* influences anthropometric measures in subjects with COPD.

GWAS of Lung Function: Relevance to COPD

Spirometric measures of lung function such as FEV_1 and FEV_1/FVC are key intermediate phenotypes of COPD. Thus, some genes that influence lung function in the general population may also be relevant to the pathogenesis of COPD. Wilk and colleagues conducted a GWAS of lung function measures in 7,691 participants in the Framingham Heart Study (FHS) with validation in an independent cohort of 835 subjects in the Family Heart Study that was enriched for airflow obstruction[73]. Four SNPs in tight linkage disequilibrium (e.g., highly correlated) on chr. 4q31were significantly associated with FEV_1/FVC percent predicted in the discovery (FHS) cohort. The association between one of the four SNPs (rs13147758) and FEV_1/FVC was replicated in the Family Heart Study, in which significant associations were also shown with FEV_1 and binary airflow obstruction phenotypes (particularly in smokers). The associated SNPs were not in a gene transcript but were near *HHIP*, a candidate gene for COPD susceptibility (see above).

In a meta-analysis of GWAS results for lung function in 20,890 participants from four CHARGE consortium studies (Atherosclerosis Risk in Communities, Cardiovascular Heath Study, FHS, and the Rotterdam Study), *HHIP* and *FAM13A* (see above) were among the eight loci associated with FEV_1/FVC (the other six were *GPR126*, *ADAM19*, *AGER-PPT2*,

PTCH1, *PID1*, and *HTR4*) at or near the threshold for GW statistical significance[74]. In a separate study, a GWAS of lung function measures was conducted in 20,288 subjects of European ancestry in the Spirometa Consortium (discovery cohort); this GWAS was then followed by a meta-analysis of data for the top signals from the discovery cohort and 32,184 subjects in the CHARGE consortium, as well as *in silico* summary association data from 21,209 individuals from the CHARGE consortium and 883 individuals in the Health 2000 Survey[75]. This study confirmed the previously reported locus on chromosome 4q31 near *HHIP* (see above) and identified five novel loci for FEV_1 or FEV_1/FVC: 2q35 in *TNS1*, 4q24 in *GSTCD*, 5q33 in *HTR4*, 6p21 in *AGER* and 15q23 in *THSD4*.

Two recent studies have assessed whether loci identified by GWAS on lung function also influence COPD. Soler-Artigas and colleagues studied a large sample of subjects of European ancestry (including individuals with and without COPD) and constructed a risk score including six SNPs in *HTR4*, *GSTCD*, *TNS1*, *AGER*, *THSD4*, and near *HHIP*[76]. Compared to subjects in a common baseline group, those in the highest risk category (estimated as approximately 5% or Europeans) had a 1.6-fold increased risk of developing COPD[76]. In another study, Castaldi et al tested whether 32 SNPs in or near 11 loci associated with lung function in prior GWAS were associated with COPD in 5,362 subjects in four cohorts (NETT-NAS, ECLIPSE, Norway, and the first 1000 subjects in COPDGene)[77]. Of the previously identified susceptibility loci for lung function, three genomic regions harbored polymorphisms associated with susceptibility to COPD at a 5% false discovery rate: the *FLJ20184*/*INTS12*/*GSTCD*/*NPNT* locus on chromosome 4q24, the chromosome 6p21 locus including AGER and PPT2, and the chromosome 5q33 locus that includes ADAM19.

Beyond GWAS

As with other complex diseases, GWAS have identified susceptibility loci that explain a modest fraction of the heritability (the proportion of variation in a phenotype due to genetic factors) of COPD, with nominal explanation of disease risk[78]. Additional work is needed for functional characterization and full assessment of variation in these susceptibility loci, as well as for understanding their individual and combined (e.g., gene-by-gene and gene-by-environment [i.e., smoking]) effects on COPD-related phenotypes.

Beyond GWAS, additional approaches to the study of COPD genetics include sequencing exomes and/or the whole genome to identify rare susceptibility variants, and conducting studies of integrative genomics (where genetic variants are evaluated for their contribution to gene expression) and epigenetics (heritable changes in gene expression that occur without changes in DNA sequence).

Genetic variants that are uncommon (minor allele frequency [MAF]=1%–4%) or rare (MAF <1%) may confer greater susceptibility to COPD in certain individuals and/or ethnic groups. Because the genotyping platforms used for GWAS of COPD predominantly include variants with MAF ≥5%, they would not be able to detect these uncommon/rare variants with moderate to strong genetic effects. Next-generation sequencing technologies provide this capability[79]. Exome sequencing allows investigators to detect rare variants in protein-coding regions of the genome. Compared to whole-genome sequencing, exome sequencing is less expensive and thus allows studying a larger number of subjects[80]. Exome sequencing has been successful in identifying the genetic etiology of a rare Mendelian disorder[81] and is currently being applied to the investigation of COPD. As prices of whole-genome sequencing drop, this will become a feasible and attractive method to detect rare variants with strong effects on COPD, particularly regulatory (non-coding) variants. Integration of data from GWAS and sequencing studies with those from studies of gene expression and

proteomics should allow researchers to focus on the most promising candidate genes for COPD susceptibility.

Studying epigenetic mechanisms (including DNA methylation, histone modification, and micro-RNA) provides a unique opportunity to examine the potential impact of demographic, environmental and lifestyle factors (e.g., diet, aging, and cigarette smoking)[82]) on gene expression in the lung and COPD. Whole-genome studies of DNA methylation, the best characterized epigenetic mechanism, and COPD are now in progress.

SUMMARY

Although much remains to be done, recent advances and the advent of new methodologies are promising and should yield increased understanding of the genetic and epigenetic mechanisms influencing the pathogenesis of COPD, both related and unrelated to severe AAT deficiency. Such understanding should ultimately be translated into novel approaches to prevent, diagnose and treat COPD.

Acknowledgments

Sources of support: Grant HL073373 from the U.S. National Institutes of Health.

REFERENCES

1. Janus ED, Phillips NT, Carrell RW. Smoking, lung function, and alpha 1-antitrypsin deficiency. Lancet. 1985; 1:152–154. [PubMed: 2857224]
2. Tobin MJ, Cook PJL, Hutchison DCS. Alpha 1-antitrypsin deficiency: The clinical and physiological features of pulmonary emphysema in subjects homozygous for Pi type Z. Brit J Dis Chest. 1983; 77:14–27. [PubMed: 6602621]
3. Silverman EK, Pierce JA, Province MA, Rao DC, Campbell EJ. Variability of pulmonary function in alpha 1-antitrypsin deficiency: Clinical correlates. Ann Intern Med. 1989; 111:982–991. [PubMed: 2596778]
4. Silverman EK, Province MA, Campbell EJ, Pierce JA, Rao DC. Variability of pulmonary function in alpha-1-antitrypsin deficiency: Residual family resemblance beyond the effect of the Pi locus. Hum Hered. 1990; 40:340–355. [PubMed: 2083948]
5. Burrows B, Knudson RJ, Cline MG, Lebowitz MD. Quantitative relationships between cigarette smoking and ventilatory function. Am Rev Respir Dis. 1977; 115:195–205. [PubMed: 842934]
6. Celedon JC, Speizer FE, Drazen JM, et al. Bronchodilator responsiveness and serum total IgE levels in families of probands with severe early-onset COPD. Eur Respir J. 1999; 14:1009–1014. [PubMed: 10596682]
7. McCloskey SC, Patel BD, Hinchliffe SJ, Reid ED, Wareham NJ, Lomas DA. Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction. Am J Respir Crit Care Med. 2001; 164:1419–1424. [PubMed: 11704589]
8. Silverman EK, Chapman HA, Drazen JM, et al. Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease: Risk to relatives for airflow obstruction and chronic bronchitis. Am J Respir Crit Care Med. 1998; 157:1770–1778. [PubMed: 9620904]
9. Laurell CB, Eriksson S. The electrophotretic a_1-globulin pattern of serum in a_1-antitrypsin deficiency. Scandinav J Clin & Lab Invest. 1963; 15:132–140.
10. Schroeder WT, Miller MF, Woo SL, Saunders GF. Chromosomal localization of the human alpha 1-antitrypsin gene (PI) to 14q31-32. Am J Hum Genet. 1985; 37:868–872. [PubMed: 3876766]
11. DeMeo DL, Silverman EK. Alpha1-antitrypsin deficiency. 2: genetic aspects of alpha(1)-antitrypsin deficiency: phenotypes and genetic modifiers of emphysema risk. Thorax. 2004; 59:259–264. [PubMed: 14985567]

12. Turino GM, Barker AF, Brantly ML, et al. Clinical features of individuals with PI*SZ phenotype of "$_1$-antitrypsin deficiency. Am J Respir Crit Care Med. 1996; 154:1718–1725. [PubMed: 8970361]
13. Dahl M, Tybjaerg-Hansen A, Lange P, Vestbo J, Nordestgaard BG. Change in lung function and morbidity from chronic obstructive pulmonary disease in a_1-antitrypsin MZ heterozygotes; a longitudinal study of the general population. Ann Intern Med. 2002; 136:270–279. [PubMed: 11848724]
14. de Serres FJ, Blanco I, Fernandez-Bustillo E. Genetic epidemiology of alpha-1 antitrypsin deficiency in North America and Australia/New Zealand: Australia, Canada, New Zealand and the United States of America. Clin Genet. 2003; 64:382–397. [PubMed: 14616761]
15. de Serres FJ. Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency: summary of an analysis of published genetic epidemiologic surveys. Chest. 2002; 122:1818–1829. [PubMed: 12426287]
16. Cichy J, Potempa J, Travis J. Biosynthesis of alpha1-proteinase inhibitor by human lung-derived epithelial cells. J Biol Chem. 1997; 272:8250–8255. [PubMed: 9079644]
17. Perlmutter DH, Cole FS, Kilbridge P, Rossing TH, Colten HR. Expression of the alpha 1-proteinase inhibitor gene in human monocytes and macrophages. Proc Natl Acad Sci U S A. 1985; 82:795–799. [PubMed: 3871944]
18. Rao NV, Wehner NG, Marshall BC, Gray WR, Gray BH, Hoidal JR. Characterization of proteinase-3 (PR-3), a neutrophil serine proteinase. Structural and functional properties. J Biol Chem. 1991; 266:9540–9548. [PubMed: 2033050]
19. Vercaigne-Marko D, Davril M, Laine A, Hayem A. Interaction of human alpha 1-proteinase inhibitor with human leukocyte cathepsin G. Biol Chem Hoppe Seyler. 1985; 366:655–661. [PubMed: 3876103]
20. Taggart C, Cervantes-Laurean D, Kim G, et al. Oxidation of either methionine 351 or methionine 358 in alpha 1-antitrypsin causes loss of anti-neutrophil elastase activity. J Biol Chem. 2000; 275:27258–27265. [PubMed: 10867014]
21. Petrache I, Fijalkowska I, Medler TR, et al. alpha-1 antitrypsin inhibits caspase-3 activity, preventing lung endothelial cell apoptosis. Am J Pathol. 2006; 169:1155–1166. [PubMed: 17003475]
22. Malhotra D, Thimmulappa R, Vij N, et al. Heightened endoplasmic reticulum stress in the lungs of patients with chronic obstructive pulmonary disease: the role of Nrf2-regulated proteasomal activity. Am J Respir Crit Care Med. 2009; 180:1196–1207. [PubMed: 19797762]
23. Nita I, Hollander C, Westin U, Janciauskiene SM. Prolastin, a pharmaceutical preparation of purified human alpha1-antitrypsin, blocks endotoxin-mediated cytokine release. Respir Res. 2005; 6:12. [PubMed: 15683545]
24. Jie Z, Cai Y, Yang W, Jin M, Zhu W, Zhu C. Protective effects of alpha 1-antitrypsin on acute lung injury in rabbits induced by endotoxin. Chin Med J (Engl). 2003; 116:1678–1682. [PubMed: 14642134]
25. Bucurenci N, Blake DR, Chidwick K, Winyard PG. Inhibition of neutrophil superoxide production by human plasma alpha 1-antitrypsin. FEBS Lett. 1992; 300:21–24. [PubMed: 1312485]
26. Janciauskiene S, Larsson S, Larsson P, Virtala R, Jansson L, Stevens T. Inhibition of lipopolysaccharide-mediated human monocyte activation, in vitro, by alpha1-antitrypsin. Biochem Biophys Res Commun. 2004; 321:592–600. [PubMed: 15358147]
27. Dafforn TR, Mahadeva R, Elliott PR, Sivasothy P, Lomas DA. A kinetic mechanism for the polymerization of alpha1-antitrypsin. J Biol Chem. 1999; 274:9548–9555. [PubMed: 10092640]
28. Lomas DA, Evans DL, Finch JT, Carrell RW. The mechanism of Z alpha 1-antitrypsin accumulation in the liver. Nature. 1992; 357:605–607. [see comments]. [PubMed: 1608473]
29. Teckman JH, Perlmutter DH. Retention of mutant alpha(1)-antitrypsin Z in endoplasmic reticulum is associated with an autophagic response. Am J Physiol Gastrointest Liver Physiol. 2000; 279:G961–G974. [PubMed: 11052993]
30. Hidvegi T, Schmidt BZ, Hale P, Perlmutter DH. Accumulation of mutant alpha1-antitrypsin Z in the endoplasmic reticulum activates caspases-4 and -12, NFkappaB, and BAP31 but not the unfolded protein response. J Biol Chem. 2005; 280:39002–39015. [PubMed: 16183649]

31. Hultcrantz R, Mengarelli S. Ultrastructural liver pathology in patients with minimal liver disease and alpha 1-antitrypsin deficiency: a comparison between heterozygous and homozygous patients. Hepatology. 1984; 4:937–945. [PubMed: 6332768]
32. Mahadeva R, Atkinson C, Li Z, et al. Polymers of Z alpha1-antitrypsin co-localize with neutrophils in emphysematous alveoli and are chemotactic in vivo. Am J Pathol. 2005; 166:377–386. [PubMed: 15681822]
33. Lomas DA, Elliott PR, Sidhar SK, et al. alpha 1-Antitrypsin Mmalton (Phe52-deleted) forms loop-sheet polymers in vivo. Evidence for the C sheet mechanism of polymerization. J Biol Chem. 1995; 270:16864–16870. [PubMed: 7622502]
34. Mulgrew AT, Taggart CC, Lawless MW, et al. Z alpha1-antitrypsin polymerizes in the lung and acts as a neutrophil chemoattractant. Chest. 2004; 125:1952–1957. [PubMed: 15136414]
35. Bernspang E, Sveger T, Piitulainen E. Respiratory symptoms and lung function in 30-year-old individuals with alpha-1-antitrypsin deficiency. Respir Med. 2007; 101:1971–1976. [PubMed: 17532199]
36. Campos MA, Wanner A, Zhang G, Sandhaus RA. Trends in the diagnosis of symptomatic patients with alpha1-antitrypsin deficiency between 1968 and 2003. Chest. 2005; 128:1179–1186. [PubMed: 16162704]
37. Parr DG, Stoel BC, Stolk J, Stockley RA. Pattern of emphysema distribution in alpha1-antitrypsin deficiency influences lung function impairment. Am J Respir Crit Care Med. 2004; 170:1172–1178. [PubMed: 15306534]
38. Campos MA, Alazemi S, Zhang G, Wanner A, Sandhaus RA. Effects of a disease management program in individuals with alpha-1 antitrypsin deficiency. COPD. 2009; 6:31–40. [PubMed: 19229706]
39. Parr DG, Guest PG, Reynolds JH, Dowson LJ, Stockley RA. Prevalence and impact of bronchiectasis in alpha1-antitrypsin deficiency. Am J Respir Crit Care Med. 2007; 176:1215–1221. [PubMed: 17872489]
40. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003; 168:818–900. [PubMed: 14522813]
41. Silverman EK, Miletich JP, Pierce JA, et al. Alpha-1-antitrypsin deficiency: High prevalence in the, St. Louis area determined by direct population screening. Am Rev Respir Dis. 1989; 140:961–966. [PubMed: 2679271]
42. DeMeo DL, Campbell EJ, Brantly ML, et al. Heritability of lung function in severe alpha-1 antitrypsin deficiency. Hum Hered. 2009; 67:38–45. [PubMed: 18931508]
43. Novoradovsky A, Brantly ML, Waclawiw MA, et al. Endothelial nitric oxide synthase as a potential susceptibility gene in the pathogenesis of emphysema in alpha1-antitrypsin deficiency. Am J Respir Cell Mol Biol. 1999; 20:441–447. [PubMed: 10030842]
44. Demeo DL, Campbell EJ, Barker AF, et al. IL10 polymorphisms are associated with airflow obstruction in severe alpha1-antitrypsin deficiency. Am J Respir Cell Mol Biol. 2008; 38:114–120. [PubMed: 17690329]
45. Castaldi PJ, DeMeo DL, Kent DM, et al. Development of predictive models for airflow obstruction in alpha-1-antitrypsin deficiency. Am J Epidemiol. 2009; 170:1005–1013. [PubMed: 19726494]
46. Carp H, Miller F, Hoidal JR, Janoff A. Potential mechanism of emphysema: alpha1-proteinase inhibitor recovered from lungs of cigarette smokers contains oxidized methionine and has decreased elastase inhibitory capacity. Proc Natl Acad Sci USA. 1982; 79:2041–2045. [PubMed: 6979049]
47. Alam S, Li Z, Janciauskiene S, Mahadeva R. Oxidation of Z {alpha}1-Antitrypsin by Cigarette Smoke Induces Polymerization: A Novel Mechanism of Early-Onset Emphysema. Am J Respir Cell Mol Biol. 2011; 45:261–269. [PubMed: 20971880]
48. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007; 176:532–555. [PubMed: 17507545]
49. Bourbeau J, Nault D, Dang-Tan T. Self-management and behaviour modification in COPD. Patient Educ Couns. 2004; 52:271–277. [PubMed: 14998597]

50. Donahue JM, Cassivi SD. Lung volume reduction surgery for patients with alpha-1 antitrypsin deficiency emphysema. Thorac Surg Clin. 2009; 19:201–208. [PubMed: 19662962]
51. Corda L, Bertella E, La Piana GE, Boni E, Redolfi S, Tantucci C. Inhaled corticosteroids as additional treatment in alpha-1-antitrypsin-deficiency-related COPD. Respiration. 2008; 76:61–68. [PubMed: 18319586]
52. Petrache I, Hajjar J, Campos M. Safety and efficacy of alpha-1-antitrypsin augmentation therapy in the treatment of patients with alpha-1-antitrypsin deficiency. Biologics. 2009; 3:193–204. [PubMed: 19707408]
53. Chapman KR, Stockley RA, Dawkins C, Wilkes MM, Navickis RJ. Augmentation therapy for alpha1 antitrypsin deficiency: a meta-analysis. COPD. 2009; 6:177–184. [PubMed: 19811373]
54. Gotzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. Cochrane Database Syst Rev. 2010 CD007851.
55. Brantly ML, Spencer LT, Humphries M, et al. Phase I trial of intramuscular injection of a recombinant adeno-associated virus serotype 2 alphal-antitrypsin (AAT) vector in AAT-deficient adults. Hum Gene Ther. 2006; 17:1177–1186. [PubMed: 17115945]
56. Somers A, Jean JC, Sommer CA, et al. Generation of transgene-free lung disease-specific human induced pluripotent stem cells using a single excisable lentiviral stem cell cassette. Stem Cells. 2010; 28:1728–1740. [PubMed: 20715179]
57. Smolonska J, Wijmenga C, Postma DS, Boezen HM. Meta-analyses on Suspected COPD Genes - A Summary of 20 Years' Research. Am J Respir Crit Care Med. 2009
58. Hunninghake GM, Cho MH, Tesfaigzi Y, et al. MMP12, lung function, and COPD in high-risk populations. N Engl J Med. 2009; 361:2599–2608. [PubMed: 20018959]
59. Pillai SG, Ge D, Zhu G, et al. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. PLoS Genet. 2009; 5 e1000421.
60. Silverman EK, Palmer LJ, Mosley JD, et al. Genomewide linkage analysis of quantitative spirometric phenotypes in severe early-onset chronic obstructive pulmonary disease. Am J Hum Genet. 2002; 70:1229–1239. [PubMed: 11914989]
61. Warburton D, Bellusci S, De Langhe S, et al. Molecular mechanisms of early lung specification and branching morphogenesis. Pediatr Res. 2005; 57:26R–37R.
62. Vestbo J, Anderson W, Coxson HO, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). Eur Respir J. 2008; 31:869–873. [PubMed: 18216052]
63. Cho MH, Boutaoui N, Klanderman BJ, et al. Variants in FAM13A are associated with chronic obstructive pulmonary disease. Nat Genet. 2010; 42:200–202. [PubMed: 20173748]
64. Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. COPD. 2010; 7:32–43. [PubMed: 20214461]
65. Kong X, Cho MH, Anderson W, et al. Genome-wide Association Study Identifies BICD1 as a Susceptibility Gene for Emphysema. Am J Respir Crit Care Med. 2011; 183:43–49. [PubMed: 20709820]
66. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004; 350:1005–1012. [PubMed: 14999112]
67. Pillai SG, Kong X, Edwards LD, et al. Loci identified by genome-wide association studies influence different disease-related phenotypes in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010; 182:1498–1505. [PubMed: 20656943]
68. Amos CI, Wu X, Broderick P, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet. 2008; 40:616–622. [PubMed: 18385676]
69. Saccone NL, Culverhouse RC, Schwantes-An TH, et al. Multiple independent loci at chromosome 15q25.1 affect smoking quantity: a meta-analysis and comparison with lung cancer and COPD. PLoS Genet. 2010; 6
70. Young RP, Whittington CF, Hopkins RJ, et al. Chromosome 4q31 locus in COPD is also associated with lung cancer. Eur Respir J. 2010; 36:1375–1382. [PubMed: 21119205]

71. Li X, Howard TD, Moore WC, et al. Importance of hedgehog interacting protein and other lung function genes in asthma. J Allergy Clin Immunol. 2011; 127:1457–1465. [PubMed: 21397937]
72. Wan ES, Cho MH, Boutaoui N, et al. Genome-Wide Association Analysis of Body Mass in Chronic Obstructive Pulmonary Disease. Am J Respir Cell Mol Biol. 2011; 45:304–310. [PubMed: 21037115]
73. Wilk JB, Chen TH, Gottlieb DJ, et al. A genome-wide association study of pulmonary function measures in the Framingham Heart Study. PLoS Genet. 2009; 5 e1000429.
74. Hancock DB, Eijgelsheim M, Wilk JB, et al. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. Nat Genet. 2010; 42:45–52. [PubMed: 20010835]
75. Repapi E, Sayers I, Wain LV, et al. Genome-wide association study identifies five loci associated with lung function. Nat Genet. 2010; 42:36–44. [PubMed: 20010834]
76. Soler Artigas M, Wain LV, Repapi E, et al. Effect of 5 Genetic Variants Associated with Lung Function on the Risk of COPD, and their Joint Effects on Lung Function. Am J Respir Crit Care Med. 2011
77. Castaldi PJ, Cho MH, Litonjua AA, et al. The Association of Genome-Wide Significant Spirometric Loci with COPD Susceptibility. Am J Respir Cell Mol Biol. 2011
78. Cookson WO, Moffatt MF. Genetics of complex airway disease. Proc Am Thorac Soc. 2011; 8:149–153. [PubMed: 21543792]
79. Cirulli ET, Goldstein DB. Uncovering the roles of rare variants in common disease through whole-genome sequencing. Nat Rev Genet. 2010; 11:415–425. [PubMed: 20479773]
80. Ng SB, Turner EH, Robertson PD, et al. Targeted capture and massively parallel sequencing of 12 human exomes. Nature. 2009; 461:272–276. [PubMed: 19684571]
81. Ng SB, Bigham AW, Buckingham KJ, et al. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nat Genet. 2010; 42:790–793. [PubMed: 20711175]
82. Yang IV, Schwartz DA. Epigenetic control of gene expression in the lung. Am J Respir Crit Care Med. 2011; 183:1295–1301. [PubMed: 21596832]

Table 1

Genome-wide Association Studies of COPD and COPD-related Phenotypes

Reference	Study Design	Results	Limitations
Pillai SG, et al. (2009)[59]	GWAS of COPD in 1,633 participants in a case-control study in Norway, with subsequent replication of top results in additional cohorts (ICGN, NETT-NAS, and BEOCOPD)	**1** Two SNPs in the *CHRNA3/CHRNA5/IREB2* locus on chromosome (chr.) 15 (rs803491 and rs1051730) were significantly associated with COPD in two replication cohorts (ICGN and NETT-NAS) and in a combined analysis including the discovery (Norway) cohort **2** These SNPs were also associated with lung function in ICGN and BEOCOPD	**1** No genome-wide significant association with any SNP in the discovery cohort **2** No functional data
Cho MH, et al. (2010)[63]	GWAS of COPD in 4,320 subjects in three case-control studies: Norway, NETT-NAS, and ECLIPSE. Replication was attempted in the COPDGene, BEOCOPD and ICGN studies.	A SNP in *FAM13A*, rs7671167, was significantly associated with COPD in the discovery cohort and in two of three replication cohorts (combined $P=1.2 \times 10^{-11}$, combined odds ratio for case-control studies 0.76, 95% confidence interval 0.69–0.83).	**1** No functional data
Kong X, et al. (2011)[65]	GWAS of percent emphysema detected by computed tomography (CT) in the Norway, ECLIPSE, and NETT studies.	**1** A SNP (rs10844154) in *BICD1* on chr. 12 was significantly associated with emphysema in the meta-analysis of the three cohorts (OR for at least mild emphysema=1.46, $P= 5.2 \times 10^{-7}$ and OR for at least moderate emphysema=1.56, $P=4.8 \times 10^{-8}$) **2** Strongest signals came from radiologist scoring rather than density mask analysis	**1** No GW significant association with emphysema in any of the three individual cohorts **2** No functional data
Wan E, et al. (2011)[72]	GWAS of body mass index (BMI) in ~3,000 subjects with COPD in three cohorts: ECLIPSE, Norway, and NETT, with replication attempted in 502 subjects in COPDGene. A GWAS of fat-free mass index (FFMI) in COPD subjects was conducted in ECLIPSE and Norway	SNP rs8050136, located in the intron of the fat mass and obesity–associated gene (*FTO*) was significantly associated with BMI $P=4.97 \times 10^{-7}$) and FFMI ($p = 1.19 \times 10^{-7}$) in the discovery cohort. Findings for BMI were replicated in COPDGene ($P=6 \times 10^{-3}$).	**1** No functional data

SNP = single nucleotide polymorphism
ICGN = International COPD Genetics Network
NETT = National Emphysema Treatment Trial
NAS = Normative Aging Study
BEOCOPD = Boston Early-Onset COPD
Genetic Epidemiology of COPD: COPDGene Study
HRCT = high resolution computed tomography of the thorax