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Pharmacogenetics of chronic obstructive pulmonary disease: challenges and opportunities

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Abstract

Similar to other common chronic diseases, chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder with multiple disease subtypes. Candidate gene studies have found genetic associations for COPD-related phenotypes that may be relevant for pharmacogenetics studies, including lung function decline and COPD exacerbations. However, few COPD pharmacogenetics studies have been completed. Most studies have focused on the role of variants in the β_2 -adrenergic receptor gene on bronchodilator response, but the findings have been inconclusive. Candidate gene studies highlight the concept that genes for COPD susceptibility may also be relevant in COPD pharmacogenetics. Currently, there are no clinical applications of pharmacogenetics to COPD therapy, but the use of pharmacogenetics to determine initial smoking cessation therapy may be closer to clinical application.

Keywords

bronchodilator response; chronic obstructive pulmonary disease; emphysema; exacerbation; pharmacogenetics; smoking cessation; SNP

Chronic obstructive pulmonary disease (COPD) is a common chronic lung condition, which may be asymptomatic in its early stages but usually causes symptoms such as shortness of breath, cough and sputum production in later stages. In developed countries, cigarette smoking is the major risk factor for COPD, although other environmental exposures may also be important. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) provides a framework for the diagnosis, staging and management of COPD [1]. The GOLD definition relies on lung function tests, specifically the forced expiratory volume in 1 s (FEV₁) and the ratio of FEV₁ to the forced vital capacity (FVC), to define COPD and to grade disease severity.

In the USA, in 2000, approximately 10 million adults reported being diagnosed with COPD by a physician [2]; however, the third National Health and Nutrition Examination Survey estimated that 24 million adults have abnormal pulmonary function consistent with COPD, revealing substantial underdiagnosis [2]. In 2000, COPD was the fourth leading cause of death

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in the USA, and mortality due to COPD has been increasing, especially in women [3]. Direct and indirect costs of COPD in the USA are estimated to be US\$42.6 billion annually, of which 6.2 billion is spent on prescription medications [3].

Treatment of COPD includes medications and nonpharmacologic interventions [4]. Smoking cessation in COPD patients who are current smokers and long-term oxygen therapy in hypoxemic COPD patients have been shown to improve survival [5–7]. Pulmonary rehabilitation, a supervised exercise and education program, has been shown to reduce symptoms and improve exercise tolerance in COPD patients [8], and influenza and pneumococcal vaccinations may reduce complications [9,10]. Inhaled bronchodilators (e.g., β -agonists and anticholinergics) and inhaled corticosteroids (ICSs) are the most commonly used medications in the management of patients with stable COPD. However, many COPD patients remain symptomatic despite medical therapy. Surgical treatments, such as lung volume-reduction surgery (LVRS) and lung transplantation, are reserved for the most severe patients [11,12]. Yet there remains a need for additional therapies for the majority of COPD patients. Genetic studies have the potential to identify novel drug targets for COPD, and pharmacogenetics may identify which COPD patients are most likely to respond to both current and novel COPD treatments.

Heterogeneity of COPD phenotypes

The GOLD definition simplifies the clinical diagnosis of COPD, but fails to fully embrace the heterogeneous nature of COPD. Multiple processes contribute to the final outcome of airflow obstruction that defines COPD. The classic dichotomy of COPD subtypes includes emphysema, characterized by destruction of the lung tissue, and chronic bronchitis, characterized by inflammation of the large airways [13–15]. Small airway disease is also an important cause of airflow obstruction [16]. However, these major COPD phenotypes may co-exist in the same patient, and there are likely to be important subphenotypes based on combinations of these and other processes. The heterogeneity of COPD and COPD phenotypes is becoming increasingly recognized [17,18]. Rennard and Vestbo have even suggested that COPD is actually a syndrome encompassing many rare diseases [19].

Recognition of the heterogeneity in COPD phenotypes is especially critical for genetic and pharmacogenetic studies (Box 1). There may be some genes that contribute to COPD in general, while other genes may be relevant only for a particular phenotype. Several papers showing candidate gene associations with emphysema highlight this point [20–22]. Severe α 1-antitrypsin (AAT) deficiency is the only clearly defined genetic cause of COPD, accounting for 1–2% of COPD cases in the USA [23]. This clinically important subtype of COPD is defined by mutations in a single gene. There are likely to be other genes that define additional relevant COPD subtypes, although these genes are likely to be of much smaller effect than AAT.

α 1-antitrypsin deficiency also provides an example of the significance of COPD subtypes in COPD pharmacogenetics. Intravenous infusion of pooled human AAT is indicated for augmentation therapy in patients with severe AAT deficiency and COPD, but not in COPD patients without this genetic subtype [24]. Conceivably, other COPD therapies may be more or less effective in patients with particular COPD-related phenotypes, although clinical trials to date have not fully addressed this heterogeneity. If these COPD phenotypes are genetically determined, then the relevant genes will be important markers of response to therapy (Figure 1). COPD pharmacogenetics studies must consider these disease-susceptibility and disease-modifying genes, in addition to genes involved in drug absorption, distribution, metabolism and excretion, or genes coding for drug targets, which have been the object of traditional pharmacogenetics studies for other diseases.

Box 1**Chronic obstructive pulmonary disease phenotypes for genetics studies**

- Lung function measurements: baseline values and decline in lung function
- Chronic bronchitis: symptoms of cough and phlegm
- Frequency of chronic obstructive pulmonary disease exacerbations
- Severity and distribution of emphysema on chest CT scans
- Severity and distribution of airway disease on chest CT scans
- Bronchodilator response
- BMI and weight loss
- Exercise capacity
- Dyspnea symptoms
- Quality of life
- Hypoxemia
- Hypercapnia
- Pulmonary hypertension
- Comorbid illnesses: such as cardiovascular disease, lung cancer and depression

Heterogeneity of treatment response in COPD

The National Emphysema Treatment Trial (NETT) was one of the first large COPD clinical trials, and provided important insight into the heterogeneity in response to COPD treatment [12]. NETT was a randomized clinical trial of LVRS versus medical management in patients with emphysema and severe airflow obstruction. In NETT, clinical characteristics were used to identify a subgroup with a high risk of mortality following LVRS [25], as well as subgroups with differing benefits from LVRS, including a subgroup of patients with upper lobe predominant emphysema and low baseline exercise capacity, in whom LVRS demonstrated a survival benefit. A meta-analysis of smaller LVRS trials confirmed the benefit in patients with upper lobe predominant emphysema and low exercise tolerance [26].

In the 1980s, two landmark randomized clinical trials – the US Nocturnal Oxygen Treatment Trial [6] and the British Medical Research Council study [7] – both demonstrated a survival benefit from long-term oxygen treatment in COPD patients with severe resting hypoxemia. However, in NETT, 33.8% of nonhypoxemic patients reported long-term oxygen use, which was associated with increased mortality [27]. In these studies of LVRS and supplemental oxygen, the same COPD treatment can lead to either an increase or a reduction in mortality depending on clinical subgroups.

While LVRS and long-term oxygen treatment are reserved for patients with more severe COPD, inhaled bronchodilators are widely prescribed across all stages of COPD severity. According to the GOLD definition, the airflow obstruction in COPD is not fully reversible with bronchodilator medication; however, many COPD patients show varying degrees of bronchodilator responsiveness (BDR) on pulmonary function testing, both in research trials and in the clinic [28,29]. Variability in the absolute change in lung function after a course of oral corticosteroids in COPD patients has also been demonstrated [30]. The interindividual

variability in response to bronchodilators, corticosteroids, LVRS and supplemental oxygen does not necessarily imply that genetic factors are involved; clinical factors are probably an important predictor of treatment response in COPD. For example, ICSs may have a greater effect on the reduction of exacerbations in patients with moderate-to-severe COPD compared with mild COPD [31]. However, if there is no variability in treatment response, then there is no potential genetic influence and pharmacogenetic studies would not be warranted.

Phenotypes for pharmacogenetics studies in COPD

Owing to the heterogeneous nature of COPD, multiple phenotypes could potentially be examined as outcomes in COPD pharmacogenetics studies. Candidate gene studies have found associations with several of these baseline COPD phenotypes, unrelated to drug treatments (Table 1). According to GOLD, COPD is defined by airflow obstruction ($FEV_1/FVC < 0.7$), determined by lung function testing [1]. Lung function normally declines as part of the aging process, while accelerated lung function decline is a hallmark of COPD [32,33]. Decline in lung function over time has been a common primary or secondary end point in clinical trials of COPD therapies [34,35]. Lung function correlates with symptoms in COPD but not completely [1]. Several studies have examined genetic associations with lung function decline in COPD. For example, He and colleagues performed a case-control comparison of subjects with the fastest and slowest rate of decline in FEV_1 in smokers with COPD over 5 years of the Lung Health Study, finding association with SNPs in the *IL-6* gene [36]. These investigators have identified other candidate genes using this approach [37]. Other groups have found genetic associations with FEV_1 decline in the general population [38–41]. Although the association studies in the general population may be relevant in determining susceptibility to COPD, they may be less relevant to pharmacogenetics studies in subjects with established disease.

These studies also demonstrate one of the drawbacks of using lung function decline as an outcome in COPD studies, namely the long timeframe needed to determine the rate of decline in an individual. Furthermore, lung function does not correlate perfectly with the symptoms that a COPD patient may experience, such as shortness of breath or exercise limitation [42]. This has led to the use of other end points in COPD clinical trials [43]. One such outcome is an acute exacerbation of COPD. Patients with COPD may experience acute exacerbations, consisting of increased symptoms of shortness of breath, cough and sputum production. These symptoms are troubling to patients, and often trigger a patient to seek medical attention. COPD exacerbations are a major cause of mortality and a major source of healthcare expenditure in patients with COPD [44–47]. In research studies, COPD exacerbations can be determined by symptom-based or event-based definitions. Symptom-based definitions rely on patient report of symptoms such as shortness of breath, cough, sputum production and wheezing [48]. Event-based definitions capture healthcare utilizations, such as prescriptions for antibiotics and/or systemic corticosteroids, urgent office or emergency room visits, and hospital admissions [49,50].

Despite the clinical importance of COPD exacerbations, only a few studies have examined genetic effects on this outcome. Most of the studies have focused on genes involved in host defense, recognizing the importance of infections as a cause of COPD exacerbations [51]. Yang *et al.* found an association between polymorphisms in mannose binding lectin-2 and admissions for COPD exacerbations in 82 patients from the UK [52]; the variants were not associated with COPD susceptibility. Takabatake and colleagues found a SNP in the chemokine (C-C motif) ligand 1 (*CCL1*) gene to be associated with clinically determined exacerbations over a 2-year period in 276 male Japanese COPD patients [53]. In 389 subjects from NETT, Foreman *et al.* found association between multiple SNPs in surfactant protein B (*SFTPB*) and COPD-related emergency room visits or hospital admissions [54]. Other COPD genetics studies have examined exacerbations as a secondary outcome. SNPs in superoxide dismutase-3 (*SOD3*)

were associated with lower lung function and increased risks of COPD hospitalization and mortality in the population-based Copenhagen City Heart Study [55]. In a Danish registry, heterozygous carriers of the AAT Z allele (PI MZ) were at increased risk for hospital admission for COPD, but the risk was confined to first-degree relatives of index cases with severe AAT deficiency [56], indicating that other genetic or shared environmental factors may have contributed to increased exacerbation risk.

In addition to COPD exacerbations, other patient-centered COPD outcomes may have genetic contributions. Our group has identified variants in four genes – microsomal epoxide hydrolase (*EPHX1*), *SFTPB*, *TGFB1* and latent TGF- β binding protein-4 (*LTBP4*) – that were associated with exercise capacity, dyspnea symptoms and the multidimensional BMI, airflow obstruction, dyspnea and exercise capacity (BODE) score [57] in 304 patients with severe COPD from NETT [58]. The association between a promoter SNP in *TGFB1* and dyspnea was replicated in the family-based Boston Early-Onset COPD Study.

Quantitative analysis of chest CT scans is useful for determining phenotypes in COPD patients, specifically emphysema and airway wall thickening [59,60]. Although it may be clinically silent to patients, the change in the amount of emphysema over serial CT scans may be a marker of a drug's effect and is starting to be used as an outcome in COPD clinical trials [61]. In a small randomized trial of AAT augmentation therapy, CT densitometry was a more sensitive measure of disease progression than traditional measures, such as decline in lung function [62]. However, long timeframes and large sample sizes may still be required to detect differences in the rate of change of emphysema on chest CT scans. There is no single ideal phenotype for COPD pharmacogenetics studies; the choice of outcome may depend on the specific treatment considered. COPD exacerbations are a relevant clinical outcome, and studies using this end point may require shorter follow-up times than studies of lung function decline or progression of chest CT emphysema, although the latter may provide important anatomical insight into disease.

Published studies in COPD pharmacogenetics

Bronchodilator responsiveness

Short-acting β -agonists (SABAs) are the most commonly prescribed medications for COPD [4], so it is not surprising that the majority of COPD pharmacogenetics studies published to date have focused on immediate BDR as an outcome. Clinically, patients are defined as bronchodilator responsive if the change in FEV₁ after treatment is greater than 12% of the baseline value and greater than 200 ml [63]. However, COPD patients may vary widely in their BDR between visits, leading to a change in categorization based on this dichotomous phenotype [29]. BDR in COPD may be more appropriately described as a continuous variable. However, the best quantitative measure of BDR is not clear. BDR may be defined as a percentage of the baseline FEV₁, as a percentage of the predicted value for FEV₁, or as an absolute volume in liters [64].

All three of these measures were used in a linkage analysis of BDR in the Boston Early-Onset COPD Study [65]. In this study, extended pedigrees were enrolled through a proband with severe airflow obstruction at less than 53 years of age. Heritability of the three BDR traits ranged between 10.1 and 26.3%. In a genome-wide linkage analysis of 560 individuals in 72 pedigrees, using 377 short tandem repeat markers, no significant or suggestive evidence of linkage to BDR was found. Regions on chromosomes 4p, 4q and 3q had logarithm of the odds of linkage scores greater than 1.0 for linkage to BDR measures, which may imply the presence of relevant genes in these regions.

β_2 -adrenergic receptor in COPD pharmacogenetics

Given the lack of strong linkage evidence, most COPD pharmacogenetics studies of acute BDR have focused on the β_2 -adrenergic receptor, the target for SABA medications (Table 2). The β_2 -adrenergic receptor (*ADRB2*) gene has two well-described coding variants (Arg16Gly and Gln27Glu) that have been extensively studied in asthma pharmacogenetics [66]. Studies in asthmatic subjects suggest that Arg16 carriers, especially homozygotes, may have increased acute BDR but worse lung function following chronic treatment with SABAs [67]. However, not all studies have consistently replicated these results.

Several groups have examined these and other *ADRB2* polymorphisms in relation to BDR in COPD patients (Table 2). Joos *et al.* genotyped the codon 16 and 27 variants in 587 smokers with mild-to-moderate COPD from the NHLBI Lung Health Study (LHS) [68]. Neither variant was associated with BDR, bronchial hyperresponsiveness or lung function decline in a case-control comparison of the 282 subjects with the fastest rate of lung function decline over 5 years of the LHS and the 305 subjects with the slowest rate of decline. Hizawa and colleagues examined 246 Japanese COPD patients with a range of disease severity, finding the Arg16 allele to be associated with lower BDR [69]. The Arg16-Gln27 haplotype was also associated with reduced BDR. In 107 Slovakian inpatients with an acute COPD exacerbation, Mokry *et al.* did not find an association between the codon 16 and 27 variants and BDR [70].

As part of a larger candidate gene study, Kim and colleagues genotyped a total of six SNPs in the *ADRB2* gene [28]. In 389 subjects with emphysema and severe airflow obstruction from NETT, two synonymous coding variants were associated with BDR. Individually, the codon 16 and 27 variants were not significant, but haplotypes of the two SNPs were marginally associated with one of the measures of BDR. Neither the two synonymous SNPs nor the codon 16 and 27 haplotype associations were associated with BDR in 949 individuals in 127 families from the Boston Early-Onset COPD Study.

ADRB2 variants have also been examined for their effects on responses to other COPD therapies. Over a 12-week study, Kim *et al.* followed 104 COPD patients from Korea who were treated with a combination of inhaled long-acting β -agonist and ICS [71]. The codon 16 and 27 variants were not associated with BDR at baseline or change in FEV₁ over 12 weeks of treatment. Umeda and coworkers treated 44 COPD patients with 8 weeks of inhaled tiotropium after a 4-week run-in period [72]. Arg16 homozygotes had a significant increase in FEV₁ over the 12 weeks.

At this point, the evidence for the role of *ADRB2* variants as pharmacogenetic determinants of response to COPD therapies is conflicting. These studies have shown only limited replication, which is common throughout complex trait genetics. Multiple factors have been proposed for the lack of replication in genetic studies [73,74], and these are also applicable to COPD pharmacogenetics studies. Many of the studies have been limited by small sample sizes and have considered only two SNPs in the gene. The heterogeneity in study populations, both in terms of race/ethnicity and COPD severity, also makes it difficult to draw firm conclusions. There have not been enough long-term studies to determine the effect of *ADRB2* SNPs on response to other therapies, such as long-acting β -agonists or tiotropium.

Other COPD pharmacogenetics studies

In addition to *ADRB2*, other candidate genes have been analyzed in COPD pharmacogenetics studies (Table 3). Zhang and colleagues identified an insertion-deletion polymorphism in the hematopoietic cell kinase (*HCK*) gene that was associated with Hck protein levels in normal subjects [75]. In 487 LHS participants, the polymorphism was not associated with a decline in lung function but was associated with BDR in a secondary analysis. As part of the candidate

gene analysis that included *ADRB2*, Kim *et al.* also examined SNPs in five candidate genes that had been previously associated with COPD or related traits – *EPHX1*, *SFTPB*, *TGFB1*, serpin peptidase inhibitor E2 (*SERPINE2*) and glutathione *S*-transferase pi (*GSTP1*) [28]. In 389 NETT subjects, three SNPs in *EPHX1* and three SNPs in *SERPINE2* were associated with various BDR phenotypes, in addition to the associations found for the two synonymous variants in *ADRB2*. A single SNP downstream from the *EPHX1* gene (which was actually a coding SNP in neighboring gene *KIAA0792*) showed replicated association with BDR in the Boston Early-Onset COPD Study families.

In patients with asthma, variants of the corticotropin-releasing hormone receptor-1 (*CRHR1*) are an important determinant of response to ICS treatment [76]. A total of 87 COPD patients were genotyped for three SNPs previously associated with ICS response in asthma [77]. One intronic variant (rs242941) was associated with change in FEV₁ after 12 weeks of treatment with ICS combined with a long-acting β -agonist.

Although not a pharmacotherapy, LVRS is an accepted treatment for selected patients with emphysema. NETT, a randomized clinical trial of LVRS versus medical management, clearly demonstrated heterogeneity in response to this COPD treatment [12]. Clinical characteristics were used to identify a subgroup with a high risk of mortality following LVRS [25], as well as subgroups with differing benefits from LVRS, including a subgroup of patients with upper lobe predominant emphysema based on chest CT scans and low baseline exercise capacity, in whom LVRS demonstrated a survival benefit, making LVRS one of the few therapies shown to alter the natural history of COPD. We genotyped five COPD candidate genes – *EPHX1*, *GSTP1*, *SERPINE2*, *SFTPB*, *TGFB1* – in 203 LVRS-treated subjects in NETT [78]. A SNP upstream from *GSTP1* and a coding and a promoter SNP in *EPHX1* were each associated with improved LVRS response, measured by reduction in the multidimensional BODE score. One additional SNP in *GSTP1* and three additional SNPs in *EPHX1* were associated with additional LVRS outcomes. In this study and in the paper by Kim [28], the candidate genes associated with treatment response were unlikely to play a direct role in drug pathways, in the case of BDR, or surgical response, in the case of LVRS. These genes may be marking COPD subtypes that may have different responses to different therapies. However, more research is needed to define these potential genetic subtypes of COPD, and to identify genes that are associated with variable response to medical and surgical therapy for COPD.

Genetic factors that affect the response to LVRS have also been investigated using genome-wide gene-expression profiling. The availability of surgically resected lung tissue makes this an attractive approach. Spira *et al.* determined a set of 17 genes that differentiated nine patients who had an improvement in BODE score at 6 months following LVRS from five patients whose BODE score was unchanged or worsened [79]. None of the candidate genes from Hersh *et al.* [78] were included in this gene set.

Pharmacogenetics of smoking cessation

Cigarette smoking is the major environmental risk factor for COPD, and smoking cessation has been clearly demonstrated to reduce the rate of lung function decline and the mortality rate in COPD [5]. Multiple studies have demonstrated genetic effects on smoking behaviors and smoking cessation, including a genome-wide association study (GWAS) that identified pharmacogenetic effects on quitting success in subjects treated with bupropion or nicotine-replacement therapy [80]. Pharmacogenetic studies of the only other US FDA-approved smoking cessation therapy, varenicline, have not yet been reported. The use of pharmacogenetics to guide initial smoking cessation therapy may even be a cost-effective approach [81]. The pharmacogenetics of smoking cessation therapies have been reviewed elsewhere [82–84].

Besides the obvious effects of cigarette smoking on COPD susceptibility, there may be overlapping genetic effects for both risk factor and disease. In the first published GWAS for COPD, Pillai *et al.* found genome-wide significant evidence of association with two SNPs in the α -nicotinic acetylcholine receptor 3/5 locus (*CHRNA3/5*) on chromosome 15 [85]. The most significant SNP was not associated with smoking intensity in either the discovery population or in the replication samples. However, these same variants have also been associated with two other smoking-related diseases, lung cancer and peripheral arterial disease, in other GWAS [86–88]. One of these lung cancer GWAS also found an association between the *CHRNA3/5* locus and smoking behavior [88]; however, this was not consistent across the other two studies [86,87]. The *CHRNA3/5* locus has been identified in other genetic studies of smoking behavior, including GWAS [89]. Besides the consideration of cigarette smoking as an environmental covariate, future COPD genetics and pharmacogenetics studies must consider whether a significant gene is influencing disease susceptibility, smoking behavior or both phenotypes.

Future perspective

Many COPD patients remain symptomatic despite maximal medical therapy, highlighting the need for novel treatments for this common, chronic disease. Only a limited number of COPD pharmacogenetics studies have been performed to date, so there is clearly a need for increased research in this area, occurring in parallel with clinical trials of novel drugs for the treatment of COPD. Pharmacogenetics studies of existing COPD therapies, such as long-acting β -agonists, long-acting muscarinic antagonists, and ICSs, are also warranted. COPD is a heterogeneous disease; thus, there are likely to be drugs that are more or less effective for patients with a particular disease subtype. Future clinical trials are likely to focus on patients with specific disease-related phenotypes, such as emphysema or airway disease, based on chest CT scans. Genetic studies may also help to refine these COPD subtypes, by identifying genetic variants associated with specific disease phenotypes. Gene-expression profiling may also be an important method to distinguish molecular subtypes of COPD. Integration of gene-expression profiling with genetic association studies has been used to identify iron-responsive element binding protein 2 (*IREB2*), located on chromosome 15 near the *CHRNA3/5* locus, as a novel COPD susceptibility gene [90]. This integrative method could also be applied to COPD pharmacogenetics research.

As with pharmacogenetics studies in general, the ultimate goal of COPD pharmacogenetics studies is to allow for more personalized treatment of COPD. However, additional research will be required in order to reach this goal. To fully realize this goal, COPD clinical trials must be designed to incorporate DNA collection, detailed phenotype assessment, including chest CT scans, and appropriate samples for genomics and proteomics. This groundwork must be completed before the consideration of genotype-guided clinical trials for COPD therapies, and before the eventual translation of COPD pharmacogenetics into clinical practice.

Executive summary

Heterogeneity of chronic obstructive pulmonary disease phenotypes

- Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease and encompasses multiple subphenotypes.
- Different COPD subtypes may have different genetic contributions, and genetic and pharmacogenetic studies must consider this heterogeneity.

Heterogeneity of treatment response in COPD

- Interindividual variability in response to bronchodilators, corticosteroids, lung volume-reduction surgery and supplemental oxygen in COPD patients does not necessarily implicate a genetic effect, but may justify studies to identify clinical and genetic factors that influence treatment response.

Phenotypes for pharmacogenetics studies in COPD

- Previous studies have shown genetic associations for lung function decline, exercise capacity, symptoms and extent and distribution of emphysema on quantitative analysis of chest CT scans.
- COPD exacerbations are likely to be an important phenotype for pharmacogenetics studies.

Published studies in COPD pharmacogenetics

- Bronchodilator responsiveness
 - A genome-wide linkage study did not find significant or suggestive linkage to bronchodilator responsiveness.
- β_2 -adrenergic receptor in COPD pharmacogenetics
 - The role of *ADRB2* variants as pharmacogenetic determinants of response to short-acting bronchodilators and other COPD therapies remains unclear.
- Other COPD pharmacogenetics studies
 - Candidate genes for COPD susceptibility or COPD-related phenotypes may be relevant candidate genes for pharmacogenetics studies.

Pharmacogenetics of smoking cessation

- Smoking cessation is a cornerstone of COPD treatment, and in the future, pharmacogenetics may be useful in guiding smoking cessation therapies.
- COPD and smoking behavior may have overlapping genetic effects.

Future perspective

- Additional studies are required before pharmacogenetics will have a clinical impact on COPD treatment.

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Figure 1. Chronic obstructive pulmonary disease heterogeneity is relevant to pharmacogenetics
Treatment X is effective in chronic obstructive pulmonary disease patients with airway disease but not emphysema. SNPs 3 and 4, both of which are associated with airway disease, will appear to be determinants of treatment response if chronic obstructive pulmonary disease subtypes are not considered or are unknown.

Table 1
Genes associated with potential phenotypes for chronic obstructive pulmonary disease pharmacogenetics studies

Phenotype	Genes with significant association
Lung function decline in chronic obstructive pulmonary disease	<i>SERPINA1</i> * [37] <i>EPHX1</i> [37] <i>IL1B, IL1RN</i> [‡] [91] <i>GSTP1, GSTT1, GSTM1</i> [‡] [92] <i>MMP1</i> [93] <i>IL4RA</i> [94] <i>ADRB2</i> [68] <i>GC</i> [95] <i>HMOX1</i> [96] <i>IL6</i> [36] <i>CDC6</i> [97] <i>LEPR</i> [98]
Chronic obstructive pulmonary exacerbations	<i>SERPINA1</i> * [56] <i>MBL2</i> [52] <i>CCL1</i> [53] <i>SFTPB</i> [54] <i>SOD3</i> [55]
Exercise capacity	<i>EPHX1</i> [58] <i>LTBP4</i> [58] <i>SFTPB</i> [58]
Symptoms (e.g., dyspnea)	<i>TGFB1</i> [58]
Emphysema on quantitative chest CT scan analysis	<i>GC</i> [95] <i>MMP9</i> [21] <i>EPHX1</i> [20] <i>GSTP1</i> [20] <i>ADRB2</i> [22] <i>TGFBR3</i> [99]

* Studies of α 1-antitrypsin heterozygous carriers (PI MZ).

[‡] Combination of variants in multiple genes associated with lung function decline, but not each gene individually.

Table 2
Chronic obstructive pulmonary disease pharmacogenetics studies of the β_2 -adrenergic receptor (*ADRB2*)

Study	Treatment	Result	Ref.
<i>Studies showing association</i>			
Hizawa <i>et al.</i> (2007)	SABA	Arg16 allele was associated with lower BDR	[69]
Umeda <i>et al.</i> (2008)	LAMA	Arg16 homozygotes had significant increase in FEV ₁ at 12 weeks	[72]
Kim <i>et al.</i> (2009)	SABA	Two synonymous coding SNPs were associated with BDR in NETT, but not in the family-based study	[28]
<i>Studies showing no association</i>			
Joos <i>et al.</i> (2003)	SABA	No association between codon 16 or 27 variants and BDR	[68]
Kim <i>et al.</i> (2008)	SABA, LABA/ICS	No association between codon 16 or 27 variants and either acute BDR or 12-week change in FEV ₁	[71]
Mokry <i>et al.</i> (2008)	SABA	Haplotypes of codon 16 and 27 variants were not associated with BDR	[70]

BDR: Bronchodilator responsiveness; FEV₁: Forced expiratory volume in 1 s; ICS: Inhaled corticosteroid; LABA: Long-acting β -agonist; LAMA: Long-acting muscarinic antagonist; NETT: National Emphysema Treatment Trial; SABA: Short-acting β -agonist.

Table 3
Other genes with significant chronic obstructive pulmonary disease pharmacogenetic associations

Study	Gene	Treatment	Outcome	Ref.
Zhang <i>et al.</i> (2007)	Hemopoietic cell kinase (<i>HCK</i>)	SABA	BDR	[75]
Hersh <i>et al.</i> (2007)	Microsomal epoxide hydrolase (<i>EPHX1</i>) Glutathione <i>S</i> -transferase pi 1 (<i>GSTP1</i>)	LVRS	Change in BODE score at 6 months	[78]
Kim <i>et al.</i> (2009)	Corticotropin-releasing hormone receptor 1 (<i>CRHR1</i>)	LABA/ICS	Change in FEV ₁ at 12 weeks	[77]
Kim <i>et al.</i> (2009)	Microsomal epoxide hydrolase (<i>EPHX1</i>) Serpin peptidase inhibitor E2 (<i>SERPINE2</i>)	SABA	BDR	[28]

BDR: Bronchodilator responsiveness; BODE: BMI, airflow obstruction, dyspnea and exercise capacity; FEV₁: Forced expiratory volume in 1 s; ICS: Inhaled corticosteroid; LABA: Long-acting β -agonist; LVRS: Lung volume-reduction surgery; SABA: Short-acting β -agonist.