A genome-wide association study of COPD identifies a susceptibility locus on chromosome 19q13

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The genetic risk factors for chronic obstructive pulmonary disease (COPD) are still largely unknown. To date, genome-wide association studies (GWASs) of limited size have identified several novel risk loci for COPD at CHRNA3/CHRNA5/IREB2, HHIP and FAM13A; additional loci may be identified through larger studies. We performed a GWAS using a total of 3499 cases and 1922 control subjects from four cohorts: the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE); the Normative Aging Study (NAS) and National Emphysema Treatment Trial (NETT); Bergen, Norway (GenKOLS); and the COPDGene study. Genotyping was performed on Illumina platforms with additional markers imputed using 1000 Genomes data; results were summarized using fixed-effect meta-analysis. We identified a new genome-wide significant locus on chromosome 19q13 (rs7937, OR = 0.74, P = 2.9 × 10−9). Genotyping this single

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nucleotide polymorphism (SNP) and another nearby SNP in linkage disequilibrium (rs2604894) in 2859 subjects from the family-based International COPD Genetics Network study (ICGN) demonstrated supportive evidence for association for COPD ($P = 0.28$ and 0.11 for rs7937 and rs2604894), pre-bronchodilator FEV$_1$ ($P = 0.08$ and 0.04) and severe (GOLD 3&4) COPD ($P = 0.09$ and 0.017). This region includes $\text{CHRNA5}$, $\text{EGLN2}$, $\text{MIA}$ and $\text{CYP2A6}$, and has previously been identified in association with cigarette smoking behavior.

**INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is defined as airflow limitation that is not fully reversible and is usually caused by exposure to noxious particles or gases—predominantly cigarette smoking, though other exposures such as biomass fuels are an important cause worldwide (1). COPD does not reverse with smoking cessation, and despite efforts to curtail cigarette smoking, COPD is a leading and increasing cause of morbidity and mortality. Worldwide, it is projected to rise to rank fifth in disease burden by 2020 (1), and in the USA, it now ranks as the third leading cause of death (2). The development of COPD among smokers is not uniform; a minority of smokers develops the disease (3), and lung function response to similar levels of cigarette smoke exposure varies greatly (4). Numerous studies have demonstrated a genetic component to COPD and smoking-related changes in lung function (5–8). However, the results of many small candidate gene studies have been inconsistent (9,10). Genome-wide association studies (GWASs) of COPD (11–13) have, to date, identified three susceptibility loci that have been well replicated (14–21). We report the results of a follow-up GWAS in four cohorts that identify a new COPD susceptibility locus.

**RESULTS**

Baseline characteristics for subjects from the four cohorts: the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE); Normative Aging Study (NAS) and National Emphysema Treatment Trial (NETT); Bergen, Norway COPD Cohort (GenKOLS); and the COPD-Genes study (first 1000 subjects) are shown in Table 1. Fixed-effects meta-analysis across the four cohorts for case–control status showed no evidence of substantial deviation from the null (lambda = 1.01, Fig. 1). The most significantly associated single nucleotide polymorphisms (SNPs) were in the previously identified locus on chromosome 4 in $\text{FAM13A}$ (Table 2). However, a new genome-wide significant locus was identified on chromosome 19q13. The top P-value was at rs7937 ($\text{OR} = 0.74$, $P$-value $= 2.88 \times 10^{-9}$). There was some evidence of heterogeneity ($P$-value $= 0.15$ for Cochrane’s $Q$, $I^2 = 43.8$); however, similar results were found using a modified random-effects model (22) ($P = 3.36 \times 10^{-7}$).

We genotyped rs7937 and another nearby genome-wide significant SNP in linkage disequilibrium (LD) (rs2604894, $r^2 = 0.74$) in 983 probands and 1876 siblings from the family-based International COPD Genetics Network study (ICGN). $P$-values for the COPD affection status for the same risk allele were 0.28 and 0.11 for rs7937 and rs2604894, respectively. More significant associations were demonstrated for pre-bronchodilator FEV$_1$ ($P = 0.08$ and 0.04, respectively) and after limiting cases to Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity classifications 3 and 4 COPD ($P = 0.09$ and 0.017, respectively).

The 19q13 locus includes the genes $\text{RAB4B}$, $\text{EGLN2}$ and $\text{CYP2A6}$, and SNPs in this locus have recently been identified in a large GWAS of smoking behavior (23,24) as associated with average number of cigarettes smoked per day; rs7937 was the second-ranked association to cigarettes per day at this locus in the study by Thorgeirsson et al. (23), with a combined P-value of $2.4 \times 10^{-9}$. To explore whether our findings were due to associations with cigarette smoking behavior, we examined the relationship of rs7937 and rs2604894 with both pack-years and average number of cigarettes smoked per day separately in the case and control groups. In none of these analyses were any significant associations found; the strongest association ($P = 0.27$) was with pack-years of smoking in controls. These results are consistent with the results reported for rs7937 in the Bergen, Norway GenKOLS cohort, at this cohort was included in the GWAS by Thorgeirsson et al. (23). While these main effects were not significant, we also examined whether there was any evidence of a gene-by-cigarettes per day or pack-years interaction; none of these analyses were significant ($P > 0.1$).

At chromosome 19q13, and at the three previously demonstrated genome-wide associated loci (11–13) (4q22—$\text{FAM13A}$; 4q31—$\text{HHIP}$; and 15q25—$\text{CHRNA3/CHRNA5/IREB2}$), we used the imputed marker data from the 1000 Genomes study to attempt to further refine previously determined association signals (Table 2 and Fig 2). At 4q22 and 4q31, imputed SNPs in high LD ($r^2$ of 1.0 and 0.9, respectively) with the most significant genotyped association had only marginally smaller P-values. At 15q25, the top hit was rs11858836; this SNP is in strong LD with the previously reported rs8034191 and rs1051730 ($r^2$ of $\sim 0.75–0.8), both part of locus 1 of Saccone et al. (25), but also in moderate LD ($r^2 = 0.4$) with rs13180, our previously reported most significant SNP in this region. We also attempted to assess whether any known non-synonymous SNPs could account for these association signals. At only one locus, 15q25, was there any non-synonymous SNP at an $r^2$ of $> 0.5$ with the most significant SNP in the region; this was the $\text{CHRNA5}$ SNP rs16969968, which has been described as part of locus 1 above. To evaluate the potential effect of rarer SNPs—those with low $r^2$ but high D—we additionally evaluated SNPs with $D > 0.8$ within 500 kb of the top four loci. Two other imputed SNPs had $D \sim 1$ with rs7937 at 19q13 and nominal associations with COPD: rs1801272 in $\text{CYP2A6}$...
Table 1. Baseline characteristics (mean ± SD or percentage)

<table>
<thead>
<tr>
<th></th>
<th>COPDGene Cases</th>
<th>Controls</th>
<th>ECLIPSE Cases</th>
<th>Controls</th>
<th>NETT/NAS Cases</th>
<th>Controls</th>
<th>GenKOLS Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>499</td>
<td>501</td>
<td>1764</td>
<td>178</td>
<td>373</td>
<td>425</td>
<td>863</td>
<td>808</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.77 (8.12)</td>
<td>60.2 (8.66)</td>
<td>63.63 (7.1)</td>
<td>57.48 (9.44)</td>
<td>67.47 (5.78)</td>
<td>69.8 (7.49)</td>
<td>65.53 (10.03)</td>
<td>55.62 (9.71)</td>
</tr>
<tr>
<td>Pack-years (years)</td>
<td>54.76 (26.69)</td>
<td>38.87 (21.07)</td>
<td>50.29 (27.42)</td>
<td>32.11 (24.84)</td>
<td>66.43 (30.68)</td>
<td>40.66 (27.85)</td>
<td>31.98 (18.46)</td>
<td>19.66 (13.58)</td>
</tr>
<tr>
<td>Average cigarettes per day</td>
<td>27.58 (11.76)</td>
<td>24.89 (11.18)</td>
<td>25.54 (12.39)</td>
<td>21.87 (11.35)</td>
<td>32.55 (13.47)</td>
<td>29.27 (14.33)</td>
<td>15.6 (7.71)</td>
<td>13.82 (7.44)</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>48.73 (18.41)</td>
<td>97.98 (11.32)</td>
<td>47.63 (15.62)</td>
<td>107.83 (7.38)</td>
<td>9.99 (13.2)</td>
<td>50.63 (17.44)</td>
<td>94.91 (9.24)</td>
<td></td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>49.5</td>
<td>50.1</td>
<td>67.0</td>
<td>57.9</td>
<td>63.8</td>
<td>100.0</td>
<td>60.1</td>
<td>50.1</td>
</tr>
</tbody>
</table>

![Figure 1](https://example.com/figure1.png)

**DISCUSSION**

While a familial component to COPD has been recognized for at least the last 40 years (27)—aside from the nearly-contemporaneous identification of alpha-1 antitrypsin deficiency (28)—the genetic determinants of COPD have been generally elusive. Our analysis adds an additional cohort to three prior GWASs and identifies a new genome-wide significant locus associated with COPD susceptibility at chromosome 19q13.

The 19q13 locus has demonstrated clear associations with smoking behavior, and has been shown to be associated with cigarettes per day in two large meta-analytic GWASs (23,24). An association operating through cigarette smoking is clearly the most parsimonious and most likely explanation. However, we cannot rule out the possibility that other mechanisms may also be responsible for the association to COPD that we observed. At 15q25, mediation approaches suggest that pack-years explain only ~1/4 of the association between these SNPs and COPD (29). Another gene at this locus, *IREB2*, was identified independently in part through gene expression and genetic association (30) as a candidate gene for COPD. In our data set, we were unable to show a significant association between rs7937 and cigarettes per day or pack-years in any of our study populations, and our finding persisted after inclusion of a non-synonymous SNP associated with cigarettes per day in this cohort. The 19q13 locus includes several other genes of potential interest expressed in developing animal or human lung: *RAB4B* (31), *MLA* (32), and *EGLN2* (33). *LTBP4* is ~150 kb away, and variants in this gene have been associated with functional outcomes in subjects with emphysema (34), and disruption of this gene leads to emphysema in mice (35) and in humans, as part of the Urban-Rifkin-Davis Syndrome (OMIM #613177) (36).

While future studies (both statistical analyses, such as causal modeling and mediation analysis, and functional studies) may help determine whether other genes at this locus play a role in the 19q13 association, it is highly likely that this association occurs through cigarette smoking. *CYP2A6* variants have additionally been associated with another major smoking-related disease, lung cancer (37). *CYP2A6* and, to a lesser extent, *CYP2B6* are involved in nicotine metabolism (38,39); the most significant associations in these studies are in LD with sequence variants that have been shown to reduce CYP2A6 enzyme activity, and rs7937 was associated with the levels of the major nicotine metabolite cotinine in a subset of subjects from the European Network for Genetic and Genomic Epidemiology (23). While we were able to identify a nominally significant association of cigarettes per day with a non-
The top result at each locus as well as additional genotyped SNPs at that locus are shown. *Imputed genotypes; note that imputed SNPs in this table had imputation quality ≥ 0.9.*

The identification of this 19q13 COPD locus, in conjunction with 15q25, highlights the critical contribution of variants affecting the major behavioral risk factor for COPD, cigarette smoking. This is in contrast to coronary artery disease, where despite the fact that cigarette smoking is a major risk factor (47), none of the identified genome-wide association loci to date has identified variants known to affect smoking, and a minority of the identified loci have been associated with traditional risk factors (48). Ongoing cigarette smoking causes accelerated lung function decline; conversely, smoking cessation attenuates this decline, improves respiratory symptoms and reduces overall mortality (49–52). Decreasing cigarette consumption is essential to reducing the risk of COPD, and though a subset of our subjects carry lower risk alleles, our data do not suggest that there are smokers unlikely to benefit from smoking cessation. Whether genetic testing may aid a subset of more susceptible individuals in smoking cessation efforts is unclear (53, 54).

While our GWAS is the largest reported to date for COPD, our sample size is still substantially smaller—by a factor of 10 or more—than some other complex diseases; a recent coronary artery disease GWAS included 22,233 cases (48). Thus, if the genetic architecture of COPD is similar to other complex common diseases, our study is underpowered to detect many of the likely other common variants contributing to COPD susceptibility. This lack of power may also explain why we were unable to discern independent associations at the 15q25 locus, as others have demonstrated (25); our family-based replication results may have also suffered from power limitations, or, less likely, reflect subtle stratification in our original case–control analysis (55, 56). Our study also did not directly assess for rare genetic variation, which may be an important contributor to COPD susceptibility (57), nor did we assess for copy number variation. Finally, we did not attempt to address issues of COPD heterogeneity, for example, through radiographic phenotypes (58).

Our GWAS increases the number of genome-wide significant loci associated with COPD to four. Our analysis at these risk loci, using publicly available dense sequencing data and imputation, helps refines these signals for further study and replication. These loci account for only a small fraction of the observed effect of all genetic variants in COPD risk, and we anticipate analysis of other types of genetic variation (rare variants, copy number variants) and perhaps more importantly—future collaborations to increase the available sample size (59)—will expand this list of genetic loci and improve our understanding of COPD susceptibility.
MATERIALS AND METHODS

Genotyping methods and study descriptions for three data sets: the ECLIPSE; NAS and NETT; and GenKOLS have been described previously (11,13,60–64). All cohorts were of self-described European white ancestry and genotyped on Illumina platforms (Human Hap550 or Quad610). Quality-control procedures included tests for subject missingness, discordances,
relatedness and sex; and marker missingness, discordances, singletons and Hardy-Weinberg equilibrium.

The study protocol for COPDGene (NCT00608764) has been described previously (65). Briefly, COPDGene is a multi-center genetic and epidemiologic investigation to study COPD and other smoking-related lung diseases. Participants completed a detailed protocol, including questionnaires, pre-and post-bronchodilator spirometry, high-resolution CT scanning of the
chest and blood samples for genotyping. Samples from self-described European whites were genotyped at the Center for Inherited Disease Research (CIDR) at Johns Hopkins University using the Illumina Omni Quad platform. COPDGene genotyping underwent a similar quality-control procedure: subjects were screened for missing call rates $>1\%$, relatedness by estimated identity-by-descent $>0.125$, sex discrepancies, and inbreeding coefficients $>0.2$. Markers were screened for missingness $>2\%$, minor allele frequency $<1\%$, and deviation of Hardy–Weinberg at $P < 1 \times 10^{-5}$. Out of an initial set of 1006 COPDGene subjects, only one was unable to be genotyped successfully; none of the others failed on quality-control criteria. Five additional subjects were excluded based on the presence of lung parenchymal abnormalities other than emphysema after chest CT scan review. The average per-subject genotype missing rate was 0.05%, with a maximum missing rate of 0.96%. Details on the COPDGene subjects, as well as the subjects from the other three cohorts passing initial quality-control before removal of principal component outliers are shown in Table 1.

Of the 986 763 autosomal markers in the COPDGene study successfully genotyped, 797 983 markers remained after quality-control, with $>95\%$ of these exclusions on the basis of low minor allele frequency ($<1\%$). Combining these markers with those from the other three cohorts (ECLIPSE, NETT/NAS and GenKOLS), a total of 296 201 markers were shared among all cohorts. After imputation from the 1000 Genomes study, this number increased to $\approx 6.1$ million SNPs. Analysis for and control of population stratification were also performed via principal components using EIGENSOFT2.0 (66) as previously described (13) for the ECLIPSE, NETT, NAS and GenKOLS cohorts. For COPDGene, pruned markers with a LD cutoff of 0.12 were chosen from those with a MAF $>0.05$, Illumina GC scores of $>0.8$ and present in HapMap CEU subjects. Outliers were removed over five iterations with deviations beyond 6 standard deviations, along the top 10 principal components. Significant principal components were defined using the Tracy–Widom statistic (67) as previously described (13). After removal of additional subjects with cryptic relatedness between cohorts and outliers by genetic ancestry based on principal components, 3456 cases and 1908 controls (99% of subjects) remained in the analysis. Ten ECLIPSE subjects were found to have borderline FEV1/FVC ratios but were retained in the analysis.

Genotype imputation within each study was performed using MaCH 1.0.16 (68) using 100 rounds of iterations to estimate model parameters and CEU samples from HapMap2 (69) and the 1000 Genomes Project (70) (phased CEU data, March 2010) as reference populations. Markers with an imputation $r^2 \leq 0.3$ were dropped from further analysis. Association analysis of SNPs with case–control status was performed in each cohort using logistic regression, adjusting for age, pack-years of smoking and genetic ancestry as summarized in the principal components. Imputed genotypes were analyzed in a similar manner, using SNP dosage data in PLINK 1.07 (71). Results were analyzed among the four cohorts using fixed-effect meta-analyses (72) using METAL (73) and in R 2.12 (www.r-project.org) with the meta-package. Genomic inflation factors (74) were calculated using GenABEL (75). $I^2$ and Cochran’s $Q$ were calculated to assess for heterogeneity; a secondary analysis using a modified random-effects model was also performed (22).

Replication genotyping was performed using the SEQUENOM MassARRAY MALDI-TOF mass spectrometer (Sequenom, San Diego, CA, USA). Details of the ICGN cohort used for replication have been previously described (13,58). Association analysis in ICGN was performed using PBAT 3.61 (76) using one-sided $P$-values for the same risk allele, adjusting for age and pack-years of smoking in the COPD affection status analysis, and age, pack-years, sex and height in the analysis of FEV1.

Analyses conditional on other SNPs were performed by extracting genotype dosage data (for imputed SNPs) or actual genotypes; logistic regression adjusting for significantly associated SNPs was performed in R 2.12. Calculation of the contribution of loci to sibling relative risk was obtained using overall odds ratios and minor allele frequencies (77,78). Estimation of the fraction of variance explained was calculated using logistic regression and Nagelkerke’s pseudo-$R^2$ (79) as implemented in R Design package, and alternatively using the estimates based on a liability threshold model by So et al. (80) using a prevalence of COPD in smokers of $\approx 10\%$ (81).

LD was calculated for HapMap2 and 1000 Genomes CEU data using SNAP (82). Regional association plots were created using LocusZoom (83). All positions are given in reference to the Human March 2006 (NCBI36/hg18) assembly.

**AUTHOR CONTRIBUTIONS**


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Manuscript writing: M.H.C., E.K.S.

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