ORIGINAL ARTICLE

Cluster analysis in the COPDGene study identifies subtypes of smokers with distinct patterns of airway disease and emphysema

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ABSTRACT

Background There is notable heterogeneity in the clinical presentation of patients with COPD. To characterise this heterogeneity, we sought to identify subgroups of smokers by applying cluster analysis to data from the COPDGene study.

Methods We applied a clustering method, k-means, to data from 10 192 smokers in the COPDGene study. After splitting the sample into a training and validation set, we evaluated three sets of input features across a range of *k* (user-specified number of clusters). Stable solutions were tested for association with four COPD-related measures and five genetic variants previously associated with COPD at genome-wide significance. The results were confirmed in the validation set.

Findings We identified four clusters that can be characterised as (1) relatively resistant smokers (ie, no/mild obstruction and minimal emphysema despite heavy smoking), (2) mild upper zone emphysema-predominant, (3) airway disease-predominant and (4) severe emphysema. All clusters are strongly associated with COPD-related clinical characteristics, including exacerbations and dyspnoea ($p<0.001$). We found strong genetic associations between the mild upper zone emphysema group and rs1980057 near *HHIP*, and between the severe emphysema group and rs8034191 in the chromosome 15q region ($p<0.001$). All significant associations were replicated at $p<0.05$ in the validation sample (12/12 associations with clinical measures and 2/2 genetic associations).

Interpretation Cluster analysis identifies four subgroups of smokers that show robust associations with clinical characteristics of COPD and known COPD-associated genetic variants.

Key messages

What is the key question?
- Can distinct subtypes of pulmonary damage be identified in smokers?

What is the bottom line?
- Cluster analysis in the COPDGene study identifies four clusters of smokers with distinct patterns of airway wall thickness, emphysema and emphysema distribution, and these subtypes show strong association with relevant clinical measures and known COPD-associated genetic variants.

Why read on?
- This paper demonstrates robust clustering results that identify clinically important subgroups of smokers in the largest COPD subtyping study to date.

BACKGROUND

The clinical presentation of COPD is heterogeneous. Smoking-related damage manifests as airway wall thickening, loss of small airways, emphysematous lung destruction and a range of extrapulmonary manifestations. However, these specific manifestations may vary in individual smokers. COPD heterogeneity has been broadly characterised as emphysema-predominant and airway-predominant disease,[1 2] and the varying amounts of airway obstruction and emphysema present in an individual can be described with quantitative CT measures. In addition to the emphysema-airway characterisation, additional subtypes have been proposed in an effort to further refine our understanding of smoking-related lung damage. Some of these, such as upper lobe-predominant emphysema and the 'frequent-exacerbator' subtype, have important consequences for clinical management.[3–5]

The most widely accepted current definition of COPD is that of the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2007).[6] Based primarily on spirometry, GOLD 2007 confirms the diagnosis of COPD based on FEV_1/FVC and classifies disease severity based on FEV_1. This simplicity

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has arguably led to improved recognition, diagnosis and treatment of the disease.[6 7] However, the GOLD 2007 criteria do not fully describe the heterogeneity of COPD,[8 9] and the most recent GOLD 2011 criteria add clinical characteristics to define new classes.[10] GOLD provides clear cut-offs to define presence/absence of COPD based on FEV_1 and FEV_1/FVC; however, spirometric measures, as well as associated CT scan characteristics such as emphysema, have a continuous distribution in the population, indicating that the smoking-related damage characteristic of COPD is likely a continuous process that can also be present in subjects who have not yet developed airflow obstruction meeting standard criteria.

One rationale for the simplicity of the GOLD 2007 criteria is that there is substantial overlap between different disease characteristics and among proposed subtypes. It is a challenge to synthesise the various smoking-related subtypes proposed in the literature because subtypes may overlap or be defined in ways that are not complementary. In an effort to derive data-driven COPD classifications, investigators have recently employed unsupervised machine learning approaches.[11–13] The benefit of such approaches is that they employ quantitative methods to define subtypes, but the challenge in applying these approaches for clinical subtype identification is that they are designed primarily for data exploration rather than specific hypothesis testing. As a result, the generalisability and reproducibility of machine-learned COPD subtype classifications in independent data samples has been largely unexplored.

We hypothesised that k-means, a widely used unsupervised clustering method, would identify novel, clinically relevant subtypes when applied to quantitative chest CT, spirometric and clinical measures from the COPDGene study. The COPDGene study is a large epidemiological and genetic study of over 10 000 current and former smokers with and without COPD that includes demographic and clinical information, spirometry, genome-wide single-nucleotide polymorphisms (SNP) genotyping data, and inspiratory and expiratory CT scans. We specified a priori a set of clinically relevant clinical and genetic variables that would be used only to evaluate and interpret (but not to generate) clusters, and we split our data into a training and validation set to provide rigorous assessment of the reproducibility of our results.

METHODS

Study population

The COPDGene study has previously been described in detail.[14] Briefly, between 2007 and 2011, 10 192 non-Hispanic Whites (NHW, n=6784) and African-American (AA, n=3408) smokers were enrolled in a multicentre study designed to investigate the genetic and epidemiological associations of COPD. Subjects with respiratory disease other than asthma, COPD or emphysema were excluded. All subjects had blood collected for genetic analysis, and they completed questionnaires, spirometry and chest CT scans. The institutional review boards of all participating centres approved the COPDGene study, and written informed consent was obtained from all subjects.

Sample splitting, feature selection and clustering

In order to assess the validity of cluster solutions, the COPDGene data were randomly split into equally sized training and validation sets. All subsequent model building was conducted in the training data, with the validation set used only for the validation of cluster characteristics and associations.

In this paper, we use the term *feature* to refer to a variable that is used as an input for clustering. A set of continuous input features for k-means clustering, hereafter referred to as the *comprehensive feature set*, was selected to represent key aspects of COPD-related physiology, particularly spirometry and quantitative chest CT data. Detailed feature descriptions are included in online supplemental table 1.

Since the quality of clustering results can be improved by eliminating uninformative features,[15] we used two approaches to generate filtered subsets of the comprehensive feature set using a *top factor* and a *core feature* approach. In the top factor approach, we identified factors that individually accounted for 5% or greater of the overall variance and then selected the top loading feature for each factor to constitute the *top factor set*. In the *core feature* approach, we considered spirometric and quantitative CT variables from the comprehensive feature set and filtered these variables based on Pearson correlation such that no variables in the core variable set were correlated at 0.7 or greater.

k-means clustering was performed using the k-means function in version 2.13,[16] and the stability of cluster solutions was assessed by average normalised mutual information (NMI) as assessed by fivefold cross-validation in the training data. Data were scaled and centred prior to clustering.

Evaluation of cluster significance in the training sample

To prioritise and evaluate the clinical relevance of clustering solutions, we specified a priori a set of COPD-related measures and genetic variables to test for association with cluster membership. These variables were not used as inputs to the clustering process. The COPD-related measures were BODE index, MMRC dyspnoea score, number of COPD exacerbations over the previous year and self-report of a lung-related emergency room visit or hospitalisation over the previous year (lung-related healthcare use). COPD-related measures were related to cluster membership using logistic regression or ordinal logistic regression as appropriate.

Genetic variables consisted of five SNPs previously associated with COPD at genome-wide significance (COPD SNPs—rs7671167,[17] rs1980057,[18 19] rs13180,[19] rs8034191,[19] rs7937[20]). Genetic associations with cluster membership were tested by logistic regression using the 'healthiest' cluster (ie, with the highest average FEV_1) as the reference, and comparisons with other cluster as reference were also performed. As a sensitivity analysis, all cluster associations were evaluated with and without adjustment for study centre, GOLD 2007 stage and GOLD 2011 classifications by including these as covariates in separate regression models.

Validation of cluster characteristics, clinical and genetic associations

After prioritising cluster solutions in the training sample by cluster stability and strength of clinical and genetic associations, a single clustering result was selected for independent validation. Clusters were assigned in the validation sample by assigning each subject to the closest cluster centre using the centres learned by the k-means algorithm in the training sample. T-tests were used to test for differences in average cluster characteristics between the training and validation samples, and cluster associations with the prespecified clinical and genetic measures were examined as described above. Additional details are included in the online supplement.

RESULTS

The characteristics of the training and validation samples are shown in table 1, and the samples are comparable. The

Table 1 Baseline characteristics of the training and validation data

	Training	Validation
N	4187	4101
Age	59.5 (9.0)	59.7 (9.0)
Gender, % female	46.7	45.9
Race, % African-American	32.0	31.4
FEV_1, % of predicted	76.9 (25.2)	77.1 (25.2)
FEV_1/FVC	0.67 (0.16)	0.67 (0.16)
Pack-years, median (IQR)	39.3 (28.0)	39.7 (27.0)
BMI	28.9 (6.3)	28.9 (6.1)
Emphysema at −950HU, median (IQR)	1.8 (5.8)	2.0 (6.1)
Upper/lower emphysema ratio (IQR)	0.8 (1.1)	0.8(1.2)
Segmental airway wall thickness	61.4 (3.2)	61.4 (3.3)
Upper/lower lobe emphysema difference (IQR)	−0.17 (2.0)	−0.14 (2.2)
Gas trapping (IQR)	14.5 (24.8)	14.7 (25.3)
GOLD unclassifiable*, %	12.0	12.6
Smoking controls, %	43.8	43.8
GOLD 1, %	8.3	7.7
GOLD 2, %	19.2	19.4
GOLD 3, %	11.3	11.3
GOLD 4, %	5.4	5.3

Values are mean (SD) unless otherwise noted.
*GOLD unclassifiable refers to subjects with a FEV_1% predicted <80 but FEV_1/FVC >0.7.

difference in sample size between the training and validation samples is due to differences in missing data (see online supplement).

Defining feature subsets

Factor analysis on the comprehensive feature set identified four factors that individually accounted for at least 5% of the variance in the data. Features with the top loadings for these factors were functional residual capacity (FRC) % predicted, FEV_1% predicted, CT-quantified emphysema at −950 Hounsfield units (HU) and bronchodilator responsiveness as a % of FEV_1. For the core feature set, correlation filtering yielded a set of four features—FEV_1% predicted, CT-quantified emphysema, segmental wall area% and emphysema distribution (log ratio of upper third/lower third emphysema).

Prioritising clustering solutions by cluster stability

Cluster stability for the three feature sets is shown in figure 1. Seven stable clustering solutions with NMI > 0.9 were prioritised for further evaluation. We examined the clinical and genetic associations of these seven solutions in the training sample. For the comprehensive and top factor feature sets, the highest stability results were for k=2. These solutions largely replicated the traditional COPD case–control distinction and were likely driven by the case–control design and recruitment strategy of COPDGene.

For the core feature set, highly stable clustering was observed for a range of k from 2 to 5. Figure 2 shows the characteristics of the clustering features for the k=3 to k=5 solutions and the pattern in which clusters emerge as k increases. Based on the strong pattern of cluster-specific clinical and genetic associations, the k=4 core feature (CF4) solution was selected for further validation.

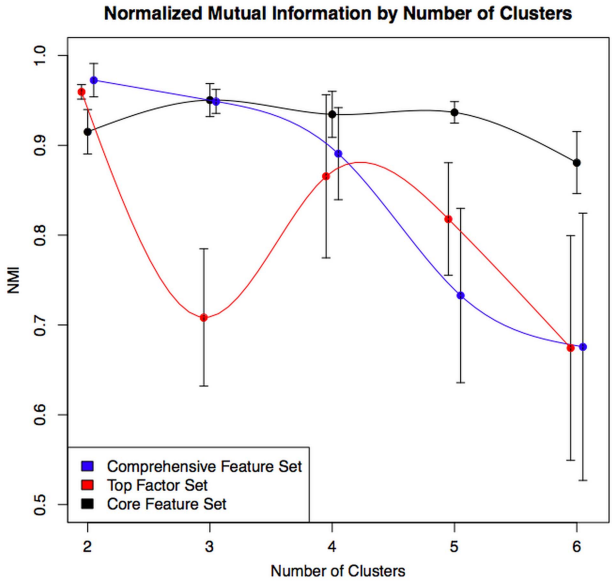

Figure 1 Cluster stability as measured by average normalised mutual information (NMI) by number of clusters across the three input feature sets. High NMI values indicate high cluster stability. For the comprehensive and top factor feature sets, stability is greatest for the k=2 solution. For the core feature set, very high stability is observed up to k=5. Dots and SEs bars represent average NMI and SEs over fivefold cross-validation, respectively. Dots are slightly offset to improve visualisation.

Cluster characteristics

Cluster characteristics for the CF4 solution are shown in table 2. The four clusters can be characterised as low susceptibility smokers, mild upper zone emphysema-predominant, airway-predominant and severe emphysema.

k=3

	C1	C2	C3
N	1833	1347	1007
FEV_1	94.7	76.0	46.0
% Emphysema	2.6	1.3	18.3
Emph Upper/Lower	1.4	0.9	3.9
Segmental WA %	58.9	63.9	62.7

1516 317 1114 843

k=4

	C1	C2	C3	C4
N	1598	623	1122	844
FEV_1	95.3	81.9	74.9	41.2
% Emphysema	2.6	3.3	1.3	20.5
Emph Upper/Lower	0.7	6.7	1.6	2.2
Segmental WA %	58.8	61.5	64.1	62.7

838 760 520 736 792

k=5

	C1	C2	C3	C4	C5
N	934	1147	531	778	797
FEV_1	96.1	91.0	80.9	67.6	40.7
% Emphysema	4.1	1.0	2.9	1.8	21.3
Emph Upper/Lower	1.0	0.5	7.5	0.7	2.3
Segmental WA %	58.0	60.7	62.0	65.1	62.6

Figure 2 Average values of clustering features from core feature set solutions k=3 through 5. Arrows indicate relationships between these k-means derived clusters that share large numbers of individuals.

Table 2 Cluster characteristics in training and validation data for core feature set cluster solution, k=4

	Training sample				Validation sample			
	C1: mean	C2: mean	C3: mean	C4: mean	C1: mean	C2: mean	C3: mean	C4: mean
N	1598	623	1122	844	1595	620	1060	826
Age	58.9	58.0*	56.8	65.4	58.7	58.9*	57.3	65.4
Gender, % female	0.44	0.53	0.52	0.40	0.43	0.51	0.53	0.40
Race, % African-American	0.30	0.46	0.37	0.19	0.29	0.45	0.37	0.17
FEV_1, per cent of predicted	95.3	81.9	74.9	41.2	95.7	81.6	73.8	42.0
FEV_1/FVC	0.76	0.70	0.71	0.42	0.76	0.69	0.71	0.42
BMI	28.7	27.9	31.4*	26.7	28.3	27.6	32.0*	26.8
Pack years	38.0	45.8	42.8	56.8	38.3	46.9	43.1	55.9
Emphysema at −950HU	2.6	3.3	1.3	20.5	2.7	3.6	1.4	20.7
Segmental airway wall thickness	58.8	61.5	64.1	62.7	58.8	61.4	64.2	63.0
Upper/lower emphysema ratio	0.7	6.7	0.6	2.2	0.7	8.3	0.6	2.3
Upper/lower emphysema difference	−0.3	1.4	−0.3	2.6	−0.3	1.7	−0.3	2.9
Gas trapping†	12.9	16.5	13.4	52.1	13.1	17.3	13.3	52.7

Values represent the mean of each variable for each cluster unless otherwise specified.
Only the variables shown in bold were used as input variables for the primary clustering solution (CF4).
*p Value comparing mean in training to validation <0.05 for t test.
†%LAA using −856 Hounsfield unit threshold on expiratory CT scan.
C1, relatively resistant smokers; C2, mild upper zone-predominant emphysema; C3, airway-predominant; C4, severe emphysema.

Cluster 1: relatively resistant smokers

Cluster 1 represents 38% of the COPDGene training sample and is characterised by heavy smoking exposure with no or minimal airflow obstruction, as well as lower emphysema ($p<0.001$ for comparison with clusters 2 and 4) and airway wall thickness ($p<0.001$ for all cluster comparisons) compared with the more severely affected clusters. The majority of individuals in the relatively resistant cluster are control smokers or GOLD stage 1 (figure 3).

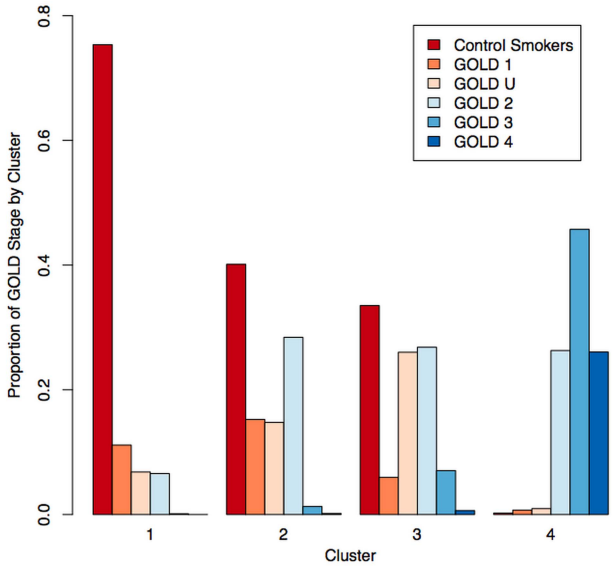

Figure 3 Proportion of individuals in each Global Initiative for Chronic Obstructive Lung Disease (GOLD 2007) stage by core feature set clustering solution (k=4). Cluster 1 (relatively smoking resistant individuals) consists largely of control smokers and GOLD 1–2 individuals. Cluster 4 (severe emphysema) consists largely of GOLD 2–4 individuals. Clusters 2 and 3 (upper zone emphysema and airway-predominant) consist largely of control smokers, GOLD 1–2 and GOLD unclassifiable (GOLD U) individuals.

Cluster 2: mild upper zone-predominant emphysema

Cluster 2 represents 15% of the training sample and is characterised by mild airflow obstruction and mild emphysema with marked upper zone-predominance (p values compared with other clusters <0.001). The average amount of emphysema in this group is modest (mean emphysema = 3.31%), though the range is broad and nearly a quarter of this cluster has greater than 5% emphysema. As shown in figure 3, most of the individuals in the mild upper zone emphysema cluster are control smokers or GOLD stages 1–2, with 15% unclassifiable by GOLD criteria.

When compared with the relatively resistant cluster, this cluster was more likely to experience an exacerbation, have a higher MMRC dyspnoea score and BODE index, and more likely to have used the emergency room or been admitted to the hospital for a respiratory issue (table 3). The NHW subjects in this group show a strong genetic association with rs1980057 near the *HHIP* gene ($p=4.4\times10^{-6}$). This cluster has a higher proportion of AAs than the airway-predominant and severe emphysema clusters ($p<0.001$) and a higher proportion of women compared with the relatively smoking-resistant and severe emphysema clusters ($p<0.001$).

Cluster 3: airway-predominant disease

Cluster 3 represents 27% of the training sample and is characterised by thicker airway walls, the lowest average emphysema of all clusters, and high BMI ($p<0.001$ for all measures). The overall distribution of GOLD 2007 stages in this group is similar to the mild upper zone emphysema cluster, with the exception of a higher proportion of GOLD stage 3 and unclassifiable individuals (figure 3).

This cluster is more likely than the relatively smoking-resistant cluster to report COPD exacerbations and lung-related healthcare use, and they have higher MMRC score and BODE index (table 3). It has a significantly higher proportion of women than the smoking-resistant and severe emphysema clusters ($p<0.001$), and the overall strength of genetic associations between this cluster and COPD SNPs is weak.

Table 3 Cluster associations with COPD-related measures and COPD SNPs in training and validation data for core feature set cluster solution, k = 4

	Training			Validation		
	C2: OR (95% CI)	C3: OR (95% CI)	C4: OR (95% CI)	C2: OR (95% CI)	C3: OR (95% CI)	C4: OR (95% CI)
Exacerbations	2.27 (1.97 to 2.61)***	3.16 (2.82 to 3.55)***	8.93 (7.97 to 10.01)***	2.17 (1.90 to 2.49)***	2.66 (2.38 to 2.98)***	7.80 (7.00 to 8.70)***
MMRC	2.81 (2.57 to 3.07)***	3.39 (3.14 to 3.66)***	10.88 (10.00 to 11.83)***	2.02 (2.01 to 2.40)***	3.00 (2.78 to 3.23)***	10.07 (9.26 to 10.94)***
BODE	3.37 (3.06 to 3.70)***	4.63 (4.27 to 5.02)***	66.52 (60.06 to 73.67)***	2.62 (2.38 to 2.88)***	4.23 (3.90 to 4.58)***	52.64 (47.62 to 58.19)***
Hospitalisations/ER visits	4.07 (3.34 to 4.95)***	5.05 (4.24 to 6.01)***	11.82 (9.98 to 14.00)***	3.05 (2.53 to 3.68)***	4.13 (3.52 to 4.86)***	8.03 (6.86 to 9.39)***
rs7671167 (FAM13A)	0.95 (0.87 to 1.04)^{NS}	0.87 (0.81 to 0.93)*	0.84 (0.78 to 0.91)*	1.01 (0.92 to 1.10)^{NS}	0.89 (0.83 to 0.95)^{NS}	0.91 (0.85 to 0.98)^{NS}
rs1980057 (HHIP)	0.64 (0.58 to 0.70)***	0.92 (0.85 to 0.98)^{NS}	0.79 (0.73 to 0.85)***	0.80 (0.73 to 0.87)*	1.09 (1.01 to 1.17)^{NS}	0.74 (0.69 to 0.80)***
rs13180 (Chr15q25)	0.82 (0.75 to 0.90)*	1.04 (0.96 to 1.11)^{NS}	0.82 (0.76 to 0.88)**	0.72 (0.66 to 0.79)***	0.99 (0.92 to 1.07)^{NS}	0.82 (0.76 to 0.88)**
rs8034191 (Chr15q25)	1.33 (1.21 to 1.46)**	1.03 (0.96 to 1.11)^{NS}	1.50 (1.39 to 1.61)***	1.30 (1.19 to 1.43)**	0.89 (0.83 to 0.96)^{NS}	1.17 (1.09 to 1.26)*
rs7937 (Chr 19q13)	1.30 (1.18 to 1.42)**	1.16 (1.08 to 1.24)*	1.20 (1.12 to 1.29)*	1.08 (0.99 to 1.18)^{NS}	1.06 (0.99 to 1.14)^{NS}	1.46 (1.36 to 1.57)***

Effect sizes represent OR from logistic regression or proportional odds logistic regression in the case of exacerbations, MMRC score and BODE index.
In all instances, cluster 1 (ie, the cluster with the highest mean FEV1% of predicted) serves as the reference.
Effect allele for rs7671167 = C, rs1980057 = T, rs13180 = C, rs8034191=C, rs7937=T.
*0.01<p≤0.05; **0.001<p≤0.01; ***p≤0.001, NS p>0.05.

Cluster 4: severe emphysema

Cluster 4 represents 20% of the sample and is characterised by high emphysema, gas trapping and severe airflow obstruction ($p<0.001$ for all measures). This group consists primarily of GOLD 2–4 individuals. It has the lowest BMI, highest lifetime pack-years exposure, oldest average age ($p<0.001$ for all measures) and it is the most severely affected cluster in terms of COPD-related measures. The effect sizes of the associations between the severe emphysema cluster and the four COPD-related clinical variables are roughly twice as large as those observed for the upper zone emphysema and airway-predominant clusters.

This cluster is strongly associated with rs1980057 ($p=0.001$) near *HHIP* and rs8034191 ($p=5\times10^{-8}$) in the chromosome 15q locus that includes the nicotinic receptor genes *CHRNA3* and *CHRNA5* as well as *IREB2* (table 3). It has a significantly higher proportion of NHWs than all other clusters and a higher proportion of male subjects than the mild upper zone emphysema and airway-predominant clusters ($p<0.001$).

Validation of the CF4 clustering solution

To validate the CF4 clustering solution, we examined the characteristics and associations of CF4 clusters in the validation data sample. The characteristics of the CF4 clusters in the training and validation samples were similar (table 2), demonstrating that the clusters can reliably be reproduced in a separate data sample.

The associations in the training and validation sample between CF4 clusters, COPD-related clinical measures and COPD SNPs are shown in table 3. For the clinical variables, all 12 of the associations are highly significant in training and validation. For the genetic risk factors, the two associations in the training sample with p values below the Bonferroni-determined threshold of $p=0.0007$ were both replicated at $p \leq 0.05$ in the validation sample. Furthermore, of the 11 genetic associations observed with $p \leq 0.05$ in the training sample, 7 were replicated at $p \leq 0.05$ in validation.

Robustness of CF4 clusters after adjustment for GOLD stage

To determine whether the associations observed with these clusters and COPD-related clinical and genetic variables were driven by severity of airflow obstruction, we repeated the cluster association tests adjusting for GOLD 2007 stage and GOLD 2011 classes A–D (see online supplemental tables 2 and 3). All of the associations with clinical measures remained significant ($p \leq 0.001$). This suggests that the discovered clusters provide information independent from COPD severity as defined by GOLD.

In regard to genetic associations, the cluster associations showed divergent behaviour in response to adjustment for GOLD 2007 stage and GOLD A–D classes. The genetic associations with cluster 4 were attenuated, whereas the strong association observed between cluster 2 (upper zone emphysema) and rs1980057 near *HHIP* was unaffected, suggesting that this association is due to properties of this cluster that are distinct from disease severity as assessed by the severity of airflow obstruction.

DISCUSSION

Using a large sample of smokers with a wide range of airflow obstruction and well characterised with respect to COPD features, cluster analysis identified solutions demonstrating strong association with clinically relevant COPD-related measures and high repeatability in cross-validation. A filtered subset of input

features yielded a four-cluster result that is informative beyond the traditional COPD case–control distinction. These clusters can be described as (1) relatively smoking-resistant individuals, (2) individuals with mild upper zone-predominant emphysema and airflow obstruction, (3) individuals with airway-predominant disease and (4) individuals with severe obstruction and emphysema. In addition to being relevant clinically, some of these clusters are strongly associated with known COPD-associated variants. These clusters and associations were validated in a second data sample from the same study population.

This analysis presents novel findings about smoking-related pulmonary subtypes. We describe a mild upper zone emphysema-predominant cluster that has not been extensively described in previous studies and demonstrate that membership in this cluster is associated with a genetic variant in the *HHIP* gene. This cluster was identified in our study population for at least three reasons: first, our study population included CT scans from a range of smokers, including those with mild or no obstruction; second, we included emphysema distribution as an input feature for clustering; and third, our sample size is substantially larger than previously reported COPD cluster analysis studies. Our work also adds to the field by explicitly addressing the reproducibility of cluster analyses and by using intrinsic (ie, cluster stability) and extrinsic (ie, clinical and genetic associations) criteria for assessing multiple potential clustering solutions.

These results confirm some of the findings from previous subtyping efforts in COPD. First, most studies have identified a severely affected group, though the severity of emphysema and airway wall thickness in this group has been variable.[12 21–23] Second, these findings affirm the concept of emphysema-predominant and airway-predominant COPD while providing additional insight regarding the role of emphysema distribution in COPD heterogeneity.[2 5 13 21 22 24 25] The identification of emphysema-predominant and airway-predominant groups, however, has not been universal. Garcia-Aymerich *et al* did not identify an airway-predominant group, and instead identified a group with elevated BMI and increased comorbidities but with less prominent airway wall thickness on CT scan.[12] In our study, the high average BMI and over-representation of women in the airway-predominant group is of clinical and epidemiological interest, and the female airway predominance recapitulates observations by Martinez *et al* in NETT.[26]

We examined the association of clusters with known COPD GWAS SNPs. While the directionality of associations varied between clusters for some SNPs, the analysed SNPs did show a consistent direction of effect compared with the previous COPD susceptibility association literature in the comparison of the relatively smoking-resistant cluster to the severe obstruction/emphysema cluster. The weak associations in our airway-predominant group are consistent with the findings in the ECLIPSE cohort, where no associations were identified with Pi10.[27] In contrast, consistent associations with the *HHIP* and 15q loci were found for the severe and mild upper lobe-predominant emphysema groups. This association in the latter group is particularly notable since the airway-predominant group, with similar average lung function to the upper lobe-predominant group, shows no strong genetic associations. These results are congruent with ECLIPSE where the associations of these loci with radiologist-scored emphysema were stronger than that for *FAM13A*.[27] Together, these findings suggest that genetic associations in COPD may be subtype dependent.

This work has some limitations. It focuses primarily on continuous spirometric and quantitative CT measures; however, other aspects of COPD such as biomarker measurements and comorbidities were not included either due to their absence from our data or due to limitations of the k-means clustering method, which can yield spurious results when applied to a mixture of continuous and categorical variables. In the future, approaches that evaluate a range of clustering methods and a wider set of variables will be of interest. However, as this work demonstrates, the inclusion of more input features does not necessarily yield better clustering results. The optimal selection of features for clustering (ie, feature selection) is a critical area for the application of unsupervised learning to disease subtyping that requires further exploration. This analysis is cross-sectional, and it is possible that these results may be confounded by differences in disease severity. This is an important limitation for all clustering efforts using cross-sectional data that could be addressed through analyses of longitudinal data or through the development of novel clustering methods. A number of subjects from the overall study were excluded from the clustering analysis due to missing data, primarily from CT scan-related variables, and there is some bias in the clustering subset compared with the excluded subjects. This limits the generalisability of the sample on which clustering was performed, though the included sample is large and consists of a broad spectrum of smoking-related disease.

In summary, k-means clustering in the COPDGene study identifies four groups of smokers that are associated with important COPD-related measures even after adjustment for GOLD stage. Genetic association analysis with known COPD-associated variants shows strong, cluster-specific associations with these known genetic risk factors. This clustering approach is reproducible in independent data sets, facilitating the further study and characterisation of these groups of smokers.

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Supplemental Materials

Methods

Data Collection

Quantitative measures of emphysema and airway wall thickness were generated with SLICER (http://www.slicer.org) and VIDA software (VIDA Diagnostics, Iowa City, IA; http://www.vidadiagnostics.com), respectively.(1) Dyspnea and lung disease-specific quality of life measures were obtained through the use of previously validated questionnaire items.(2;3)

Cross-Validation Estimates of Cluster Stability

To assess the stability of various cluster solutions, we used five-fold cross validation to derive estimates of cluster stability as quantified by the average normalized mutual information (NMI). Normalized mutual information quantifies the dependency between variables, and it ranges from 0 (no dependency) to 1 (high dependency). Unlike Pearson correlation, NMI captures nonlinear in addition to linear dependency between variables. This procedure was carried out entirely in the training portion of the data. Four-fifths of the training sample served as the cross-validation training set (CV Train) and the remaining one-fifth of the data served as cross-validation test set (CV Test). Using the learned centroids from the CV Train set, clusters were predicted in the CV Test set and then compared to the cluster results for that fold obtained by running k-means on the entire (original) training sample. NMI quantified the degree of agreement, and the average NMI results obtained from each of the five rounds of cross-validation were used to prioritize cluster solutions by stability.

Genetic Association Testing

Genetic associations were performed in non-Hispanic white (NHW) subjects only using additive genetic coding and adjusted for principal components of genetic ancestry. A Bonferonni-adjusted statistical significance of p=0.0007 for genetic associations in the training set was defined based on 70 genetic association tests performed. The threshold for validation in the independent sample was p=0.05.

Missing Data

We employed a complete cases approach and excluded individuals from analysis who were missing data in any of the variables used for clustering, cluster association testing or interpretation. There was no difference in age of pack-years between included and excluded subjects (Supplemental Table 8). There was statistically significant but relatively minor differences in FEV_1 and FEV_1/FVC, and there were significant differences in gender and racial composition. Subjects with missing data were more likely to be female and African-American. Of the 10,300 individuals enrolled in COPDGene, 108 non-smokers were excluded from analysis, as well as 63 individuals with inadequate spirometry data. Of the remaining 10,129 individuals, 511 did not receive an inspiratory or expiratory scan. An additional 953 subjects failed quality control for either the inspiratory or expiratory scan, and 64 subjects were excluded for an FRC/TLC ratio >1. Of the remaining 8,601 subjects, 143 had incomplete data for emphysema distribution. An additional 170 individuals were excluded due to missing data for the following variables: airway wall thickness (n=4), gas

trapping (n=44), resting oxygen saturation (n=2), MMRC dyspnea score (n=11), and BODE (n=109).

Supplemental Table 1. Feature Descriptions for Comprehensive Feature Set

	Variables	Descriptions
Spirometry-Defined Variables	Post-bronchodilator FEV_1 % of predicted	observed FEV_1 (liters)/predicted FEV_1 (liters) from Hankinson equations
	FVC	observed forced vital capacity (liters)
	FEV_1/FVC	observed FEV_1 (liters)/observed FVC (liters)
	BDR as % of FEV_1	% Change in FEV_1 volume: (post-bronchodilation FEV_1 - pre-bronchodilation FEV_1, liters) /post-bronchodilation FEV_1 (liters)
	BDR as % of FVC	% Change in FVC volume: (post-bronchodilation FVC - pre-bronchodilation FVC, liters) /post-bronchodilation FVC (liters)
CT-Defined Variables	log-transformed emphysema (%LAA -950HU*)	log(%LAA -950HU + 1)
	Log ratio of Upper Third to Lower Third Emphysema	log(%LAA -950 in upper third of lung/%LAA -950 in lower third of lung)
	Segmental Wall Area %	Area of airway wall/area of entire airway for 6 selected segmental level airways (RB1, RB4, RB10, LB1, LB4, LB10)
	TLC % of Predicted	TLC measured from inspiratory CT (liters)/predicted TLC (liters)
	FRC % of Predicted	FRC measured from expiratory CT (liters)/predicted FRC (liters)
	Gas Trapping	%LAA -856HU on expiratory scan
Other Physiologic Measures	BMI	weight (kg)/height (m^2)
	Oxygen Saturation	peripheral oxygen saturation, %
* HU = Hounsfield units		

Supplemental Table 2. Cluster Associations in Training Sample for CF4 Solution Adjusting for GOLD 2007 Stage

	Training					
	C2:OR	C2:pval	C3:OR	C3:pval	C4:OR	C4:pval
Exacerbations	1.62	<0.001	2.03	<0.001	2.98	<0.001
MMRC	2.24	<0.001	2.27	<0.001	2.46	<0.001
BODE	2.45	<0.001	2.54	<0.001	4.27	<0.001
Hospitalizations/ER Visits	3.15	<0.001	3.45	<0.001	3.44	<0.001
rs7671167 (*FAM13A*)	0.98	0.81	0.96	0.59	0.89	0.53
rs1980057 (*HHIP*)	0.66	7.81E-05	0.92	0.35	0.78	0.16
rs13180 (Chr15q)	0.89	0.26	1.16	0.08	1.06	0.75
rs8034191 (Chr15q)	1.19	0.09	0.90	0.22	1.13	0.49
rs7937 (Chr 19q)	1.31	0.01	1.11	0.21	1.21	0.31
OR = odds ratio. Effect sizes represent odds ratio from logistic regression or proportional odds logistic regression in the case of Exacerbations, MMRC Score, and BODE index.						

Supplemental Table 3. Cluster Associations in Training Sample for CF4 Solution Adjusting for GOLD 2011 A-D Classes

	Training					
	C2:OR	C2:pval	C3:OR	C3:pval	C4:OR	C4:pval
Exacerbations	1.75	<0.001	1.96	<0.001	2.11	<0.001
MMRC	2.19	<0.001	2.30	<0.001	4.15	<0.001
BODE	2.55	<0.001	2.93	<0.001	22.87	<0.001
Hospitalizations/ER Visits	3.28	<0.001	3.42	<0.001	4.54	<0.001
rs7671167 (*FAM13A*)	0.96	0.64	0.93	0.35	0.87	0.24
rs1980057 (*HHIP*)	0.64	1.36E-05	0.91	0.24	0.83	0.11
rs13180 (Chr15q)	0.89	0.24	1.11	0.19	0.95	0.67
rs8034191 (Chr15q)	1.21	0.06	0.92	0.31	1.28	0.04
rs7937 (Chr 19q)	1.33	0.004	1.13	0.11	1.29	0.03
OR = odds ratio. Effect sizes represent odds ratio from logistic regression or proportional odds logistic regression in the case of Exacerbations, MMRC Score, and BODE index.						

Supplemental Table 4. Cluster Associations in Training Sample Using Cluster 2 (ULP) as Reference

Response	Group	OR (CI)	P
Exacerbations	C1	0.44 (0.38-0.51)	<0.001
	C3	1.39 (1.22-1.58)	0.01
	C4	3.93 (3.47-4.46)	<0.001
BODE	C1	0.3 (0.27-0.33)	<0.001
	C3	1.37 (1.25-1.51)	<0.001
	C4	19.75 (17.72-22.03)	<0.001
MMRC	C1	0.36 (0.33-0.39)	<0.001
	C3	1.21 (1.1-1.32)	0.04
	C4	3.87 (3.52-4.26)	<0.001
Hospitalizations/ ER Visits	C1	0.25 (0.2-0.3)	<0.001
	C3	1.24 (1.06-1.45)	0.17
	C4	2.91 (2.5-3.38)	<0.001
rs7671167	C1	0.95 (0.87-1.04)	0.59
	C3	0.91 (0.83-1)	0.33
	C4	0.9 (0.82-0.99)	0.29
rs1980057	C1	0.64 (0.58-0.7)	<0.001
	C3	1.42 (1.28-1.56)	<0.001
	C4	1.21 (1.1-1.34)	0.05
rs13180	C1	0.82 (0.75-0.9)	0.03
	C3	1.29 (1.17-1.42)	0.01
	C4	1.01 (0.91-1.11)	0.93
rs8034191	C1	1.33 (1.21-1.46)	0.002
	C3	0.76 (0.69-0.84)	0.01
	C4	1.1 (1-1.22)	0.31
rs7937	C1	1.3 (1.18-1.42)	0.004
	C3	0.9 (0.81-0.99)	0.26
	C4	0.92 (0.83-1.02)	0.41
Reference cluster -= C2 (Upper Lobe Predominant)			

Supplemental Table 5. Cluster Associations in Training Sample Using Cluster 3 (AP) as Reference

Response	Group	OR (CI)	P
Exacerbations	C1	0.32 (0.28-0.36)	<0.001
	C2	0.72 (0.63-0.82)	0.01
	C4	2.82 (2.56-3.12)	<0.001
BODE	C1	0.22 (0.2-0.23)	<0.001
	C2	0.73 (0.66-0.8)	<0.001
	C4	14.37 (13.06-15.81)	<0.001
MMRC	C1	0.29 (0.27-0.32)	<0.001
	C2	0.83 (0.76-0.91)	<0.001
	C4	3.21 (2.95-3.48)	<0.001
Hospitalizations/ ER Visits	C1	0.2 (0.17-0.24)	<0.001
	C2	0.81 (0.69-0.94)	<0.001
	C4	2.34 (2.08-2.64)	<0.001
rs7671167	C1	0.32 (0.28-0.36)	0.05
	C2	0.72 (0.63-0.82)	0.33
	C4	2.82 (2.56-3.12)	0.86
rs1980057	C1	0.22 (0.2-0.23)	0.22
	C2	0.73 (0.66-0.8)	<0.001
	C4	14.37 (13.06-15.81)	0.05
rs13180	C1	0.29 (0.27-0.32)	0.62
	C2	0.83 (0.76-0.91)	0.01
	C4	3.21 (2.95-3.48)	0.004
rs8034191	C1	0.2 (0.17-0.24)	0.66
	C2	0.81 (0.69-0.94)	0.01
	C4	2.34 (2.08-2.64)	<0.001
rs7937	C1	0.32 (0.28-0.36)	0.03
	C2	0.72 (0.63-0.82)	0.26
	C4	2.82 (2.56-3.12)	0.75
Reference cluster -= C3 (Airway Predominant)			

Supplemental Table 6. Cluster Associations in Training Sample Using Cluster 4 (SE) as Reference

Response	Group	OR (CI)	P
Exacerbations	C1	0.11 (0.1-0.13)	<0.001
	C2	0.25 (0.22-0.29)	<0.001
	C3	0.35 (0.32-0.39)	<0.001
BODE	C1	0.02 (0.01-0.02)	<0.001
	C2	0.05 (0.05-0.06)	<0.001
	C3	0.07 (0.06-0.08)	<0.001
MMRC	C1	0.09 (0.08-0.1)	<0.001
	C2	0.26 (0.23-0.28)	<0.001
	C3	0.31 (0.29-0.34)	<0.001
Hospitalizations/ ER Visits	C1	0.08 (0.07-0.1)	<0.001
	C2	0.34 (0.3-0.4)	<0.001
	C3	0.43 (0.38-0.48)	<0.001
rs7671167	C1	0.84 (0.78-0.91)	0.95
	C2	0.9 (0.82-0.99)	0.10
	C3	0.99 (0.91-1.07)	0.19
rs1980057	C1	0.79 (0.73-0.85)	0.01
	C2	1.21 (1.1-1.34)	0.24
	C3	0.86 (0.8-0.93)	<0.001
rs13180	C1	0.82 (0.76-0.88)	<0.001
	C2	1.01 (0.91-1.11)	0.90
	C3	0.79 (0.73-0.86)	0.01
rs8034191	C1	1.5 (1.39-1.61)	0.004
	C2	1.1 (1-1.22)	0.13
	C3	1.42 (1.31-1.54)	0.03
rs7937	C1	1.2 (1.12-1.29)	0.38
	C2	0.92 (0.83-1.02)	0.38
	C3	1.03 (0.95-1.11)	<0.001
Reference cluster -= C3 (Airway Predominant)			

Supplemental Table 7. Comparison of Clustering Assignment in GOLD 2-4 Subjects from Clustering Performed in All Subjects and Clustering Performed in GOLD 2-4 Only

		Classification of GOLD 2-4 Subjects in All Subjects Analysis			
		C1	C2	C3	C4
Classification of GOLD 2-4 Subjects in Case Only Clustering	C1	107	179	0	0
	C2	0	0	379	1
	C3	0	7	8	827

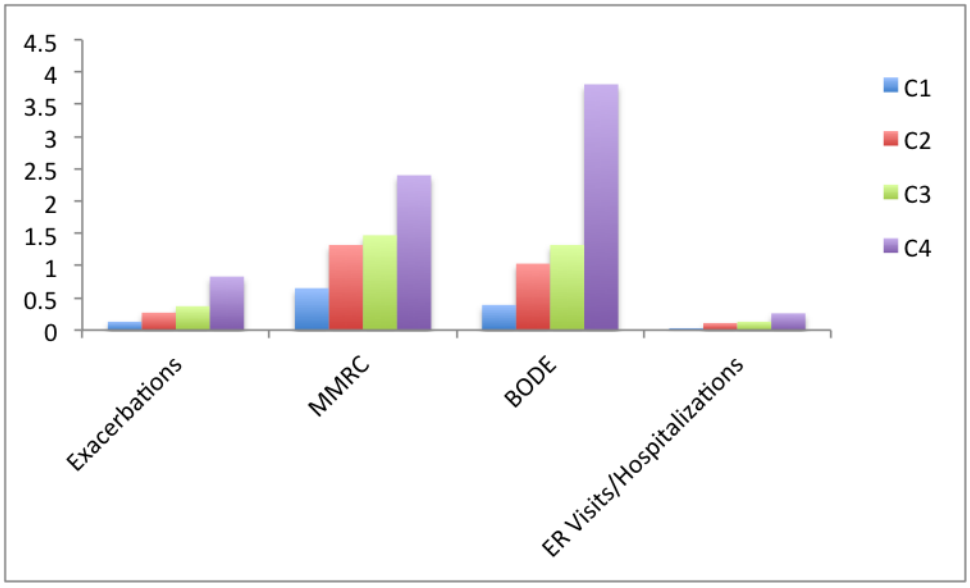
Supplemental Table 8. Characteristics of Subjects Excluded for Missing Data Compared to Analyzed Subjects

Characteristic	Subjects with Complete Data	Subjects Excluded for Missing Data	P-value
N	8288	1904	---
Gender, % Female	0.46	0.50	0.01
Race, % African-American	0.32	0.42	<0.001
Age	58.9 (14.4)	58.4 (14.8)	0.15
Pack Years	39.5 (27.8)	38.3 (26.9)	0.15
FEV_1, % of predicted	81.0 (34.3)	78.8 (39.6)	<0.001
FEV_1/FVC	0.72 (0.20)	0.71 (0.23)	0.006
63 excluded subjects were missing data for the analyzed characteristics above. P-value obtained by Pearson's chi-square test (proportions) or Wilcoxon rank sum test.			

Supplemental Table 9. Detailed Smoking Information for Training and Validation Data

Characteristic	Training	Validation
N	4187	4101
Pack-Years, median (IQR)	39.3 (28.0)	39.7 (27.0)
Smoking Intensity, median (IQR)	20 (10)	20 (10)
Smoking Duration in years	36.4 (10.1)	36.4 (10.2)
Age Started Smoking	16.9 (4.5)	16.8 (4.7)

Supplemental Figure 1. Average Number of Exacerbations of Past Year, MMRC Score, BODE Index, and Number of ER Visits and Hospitalizations by Cluster



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