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# Lobar Emphysema Distribution Is Associated With 5-Year Radiological Disease Progression



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**BACKGROUND:** Emphysema has considerable variability in its regional distribution. Cranio-caudal emphysema distribution is an important predictor of the response to lung volume reduction. However, there is little consensus regarding how to define upper lobe-predominant and lower lobe-predominant emphysema subtypes. Consequently, the clinical and genetic associations with these subtypes are poorly characterized.

**METHODS:** We sought to identify subgroups characterized by upper-lobe or lower-lobe emphysema predominance and comparable amounts of total emphysema by analyzing data from 9,210 smokers without alpha-1-antitrypsin deficiency in the Genetic Epidemiology of COPD (COPDGene) cohort. CT densitometric emphysema was measured in each lung lobe. Random forest clustering was applied to lobar emphysema variables after regressing out the effects of total emphysema. Clusters were tested for association with clinical and imaging outcomes at baseline and at 5-year follow-up. Their associations with genetic variants were also compared.

**RESULTS:** Three clusters were identified: minimal emphysema ( $n = 1,312$ ), upper lobe-predominant emphysema ( $n = 905$ ), and lower lobe-predominant emphysema ( $n = 796$ ). Despite a similar amount of total emphysema, the lower-lobe group had more severe airflow obstruction at baseline and higher rates of metabolic syndrome compared with subjects with upper-lobe predominance. The group with upper-lobe predominance had greater 5-year progression of emphysema, gas trapping, and dyspnea. Differential associations with known COPD genetic risk variants were noted.

**CONCLUSIONS:** Subgroups of smokers defined by upper-lobe or lower-lobe emphysema predominance exhibit different functional and radiological disease progression rates, and the upper-lobe predominant subtype shows evidence of association with known COPD genetic risk variants. These subgroups may be useful in the development of personalized treatments for COPD.

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**KEY WORDS:** clustering; COPD; COPD disease progression; emphysema distribution; machine learning

**ABBREVIATIONS:** COPDGene = Genetic Epidemiology of COPD; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GWAS = genome-wide association studies; HU = Hounsfield units; MMRC = Modified Medical Research Council; PCA = principal components analysis; % LAA-950 = percent of CT low attenuation area  $< -950$  HU at end-inspiration; Pi10 = square root of the wall area of a hypothetical airway of 10-mm internal perimeter; PRM =

Parametric Response Mapping; PRM-fSAD = functional small airways disease; SGRQ = St. George's Respiratory Questionnaire

**AFFILIATIONS:** From the Channing Division of Network Medicine, Department of Medicine (Drs Boueiz, DeMeo, Silverman, and Castaldi), the Pulmonary and Critical Care Medicine Division, Department of Medicine (Drs Boueiz, Cho, Washko, DeMeo, and Silverman),

Emphysema exhibits considerable heterogeneity in its extent and spatial distribution.<sup>1</sup> Although total lung emphysema is a strong predictor of many COPD-related outcomes, the craniocaudal distribution of emphysema is an independent predictor of mortality and the response to lung volume reduction.<sup>2-6</sup> Emphysema distribution is partially genetically determined, with an estimated heritability of 20%, and genome-wide association studies (GWAS) of this trait as a continuous measure have identified multiple genome-wide significant associations.<sup>7,8</sup> Thus, emphysema distribution is a COPD phenotype with both clinical and biological relevance.

Most previous studies have evaluated emphysema distribution as a continuous trait, but for treatment decisions and clinical trials, it is often useful to define groups of subjects based on specific disease characteristics. However, although there is compelling evidence that emphysema distribution is an important facet of COPD clinical heterogeneity, approaches to define groups of

subjects according to upper-lobe or lower-lobe emphysema predominance independent of other disease markers are needed to enable better characterization of these subtypes. In addition, defining emphysema distribution subgroups through the use of thresholds for an emphysema ratio often results in an imbalance in the amount of total emphysema between groups.

In the present study, we sought to identify subgroups of smokers characterized by upper-lobe or lower-lobe emphysema predominance and comparable amounts of total emphysema. We hypothesized that these emphysema distribution subtypes would have different clinical characteristics and genetic associations. To test this hypothesis, we used a data-driven clustering approach to identify upper-lobe-predominant and lower-lobe-predominant emphysema subgroups with comparable amounts of total emphysema, and we characterized these subgroups using extensive phenotypic and genotypic data from the COPDGene study at baseline and at 5-year follow-up.

## Methods

### Study Population

The COPDGene study is an ongoing large multicenter longitudinal study designed to investigate the genetic and epidemiologic characteristics of COPD. The protocols for subject recruitment and

data collection for the COPDGene study have been previously described.<sup>9</sup> During phase I, the COPDGene study enrolled 10,192 non-Hispanic white and African American subjects across the full spectrum of disease severity as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric grading system. Eight individuals had Pi ZZ or ZNull  $\alpha_1$ -antitrypsin deficiency and were excluded in this present study. During phase II, 5,000 subjects had completed their 5-year follow-up visit at the time of this analysis (COPDGene phase II data set, September 24, 2016). Nineteen of these 5,000 subjects underwent lung volume reduction surgery or lung transplantation between the two visits and were excluded from this analysis. Written informed consent was obtained from all participants. The study and consent forms were approved by the Brigham and Women's Hospital Institutional Review Board (No. 2007P000554/BWH).

### CT Measurements

Using 3D SLICER analysis ([www.chestimagingplatform.org](http://www.chestimagingplatform.org)) at visit 1 and Thirona software ([www.thirona.eu](http://www.thirona.eu)) at visit 2, emphysema was quantified as the percentage of lung voxels with attenuation lower than -950 HU at maximal inspiration (% LAA-950).<sup>10</sup> The lungs were automatically segmented into anatomically defined lung lobes, as previously described,<sup>11</sup> and % LAA-950 was quantified in each lobe. The lingula was included in the left upper lobe measurements. The ratio of % LAA-950 in both upper lobes to that in both lower lobes was used to evaluate the lobar distribution of emphysema (U/L ratio).

Airway disease was assessed using VIDA software (VIDA Diagnostics, Inc.; [www.vidadiagnostics.com](http://www.vidadiagnostics.com)) as gas trapping (percentage of low attenuation units < -856 Hounsfield units [HU] at end-expiration), airway wall thickness (obtained along the center line of the lumen, in the middle third of the airway segment, for one segmental airway of each lung lobe; the mean value across all lobes was used for analysis), and Pi10 (the square root of the wall area of a hypothetical airway of 10-mm internal perimeter).

the Surgical Planning Laboratory, Laboratory of Mathematics in Imaging, Department of Radiology (Dr Estépar), and the Division of General Medicine and Primary Care (Dr Castaldi), Brigham and Women's Hospital, Harvard Medical School, Boston, MA; the Department of Electrical and Computer Engineering (Drs Chang and Dy), Northeastern University, Boston, MA; and the Division of Pulmonary Medicine, Department of Medicine (Drs Bowler and Crapo), National Jewish Health, Denver, CO.

This work was presented in abstract form at the annual meeting of the American Thoracic Society, May 13-18, 2016, San Francisco, CA. El Boueiz A, Cho MH, Washko GR et al. Clinical and genetic characteristics of emphysema distribution subtypes identified by unsupervised learning analysis [abstract]. *Am J Respir Crit Care Med*. 2016;193:A7480.

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Although small airway disease can be assessed by gas trapping, a significant limitation of this approach is that many lung regions that trapped gas on exhalation will also show emphysematous destruction when fully inflated to total lung capacity.<sup>12</sup> We therefore also analyzed data from a recently developed CT analytic method, Parametric Response Mapping (PRM) by Imbio LLC, using Lung Density Analysis software (Imbio LLC).<sup>13</sup> By co-registering inspiratory and expiratory CT images, the PRM method discriminates emphysema (PRM-emphysema) from nonemphysematous air trapping, termed functional small airways disease (PRM-fSAD).<sup>14</sup> These PRM measurements were available for 3,073 subjects at visit 1 and 2.

### Clustering and Statistical Analyses

Emphysema variables from visit 1 were  $\log(x+1)$  transformed to reduce the impact of deviations from normality. To account for emphysema severity and generate lobe-specific measures, each lobar emphysema variable was regressed on total emphysema. Unsupervised random forest clustering was then performed on the residuals, using the approach described by Shi and Horvath.<sup>15</sup>

## Results

### Characteristics of Study Participants Included in the Analyses

We included in the analysis 9,210 smokers (6,195 non-Hispanic whites and 3,015 African Americans) with complete lobar imaging and phenotypic data from visit 1. The characteristics of these subjects are shown in e-Table 2. Compared with non-Hispanic whites, African American subjects were slightly younger and had a lower median exposure to smoking, a higher FEV<sub>1</sub> % predicted, less severe total emphysema, and less advanced COPD.

### Cluster Analysis

When the clustering variables were visualized using principal components analysis (PCA), it was apparent that subjects are spread along a continuum of emphysema distribution, and standard approaches that classify all subjects would not be guaranteed to identify a core of tightly clustered subjects (Fig 1). Based on this observation, we applied an unsupervised random forest clustering method designed to identify tightly clustered subjects and remove poorly clustered observations. This algorithm identified three clusters consisting of 3,013 subjects. Clustering criteria were not met in 6,197 subjects. The characteristics of these subjects, shown in e-Table 3, demonstrate that this “poorly clustered” group encompasses subjects across the range of COPD severity (GOLD 0-GOLD 4) with less total emphysema than either the upper lobe- predominant or lower lobe- predominant groups. Most importantly, the members of this group have neither marked upper-lobe or lower-lobe emphysema predominance (U/L ratio, 1.31 [IQR, 0.94-1.86]).

The identified clusters were tested for associations with visit 1 and visit 2 characteristics. The definitions of the various COPD characteristics and comorbidities are shown in e-Table 1. The longitudinal outcomes were calculated by subtracting the visit 1 value from the visit 2 value. Negative values represent a lower value of the outcome at visit 2.

Using PLINK, version 1.9, a GWAS was conducted comparing upper-lobe vs lower-lobe clusters adjusting for pack-years of smoking, current smoking, sex, and principal components of genetic ancestry.<sup>16</sup> Separate results in non-Hispanic white and African American subjects were combined using fixed-effects meta-analysis implemented in METAL software (August 8, 2010).<sup>17</sup> We also evaluated associations with 25 genetic variants previously associated with COPD susceptibility, emphysema, or emphysema distribution (“candidate single nucleotide polymorphism [SNP] analysis”).<sup>7,8,18-24</sup> Additional methods are available in e-Appendix.

### Visit 1 Imaging Characteristics

To determine whether these clusters did represent upper lobe-predominant and lower-lobe predominant emphysema subtypes, we evaluated the lobar emphysema values within each cluster and confirmed that the clusters were characterized by minimal emphysema ( $n = 1,312$ ), upper lobe-predominant emphysema (upper-lobe predominant cluster;  $n = 905$ ; U/L ratio: 4.60 [interquartile range [IQR], 3.31-7.08]), and lower lobe-predominant emphysema (lower-lobe predominant cluster [ $n = 796$ ]; U/L ratio, 0.50 [IQR, 0.39-0.62]) (Table 1; e-Fig 1). Despite the pronounced difference in emphysema distribution, the upper lobe-predominant and lower lobe-predominant clusters had a similar extent of total emphysema (5.4 [IQR, 2.4-13.8] vs 5.5 [IQR, 2.2-16.7];  $P = .85$ ) (e-Fig 1). No difference in airway wall thickening or Pi10 was noted among the three clusters, but both upper lobe-predominant and lower lobe-predominant subjects had more gas trapping compared with subjects with minimal emphysema. e-Table 4 includes detailed characteristics of these subgroups.

### Visit 1 Demographic, Physiological, and Clinical Characteristics

Relative to subjects with upper-lobe predominance, those in the lower-lobe cluster were slightly older, more likely to be non-Hispanic white, had more severe airway obstruction, and had a higher prevalence of metabolic syndrome. There was no significant difference between the upper-lobe and lower-lobe clusters regarding smoking exposure and exacerbation frequency (Table 1). The “minimal emphysema” cluster contained predominantly female subjects with fewer pack-years of

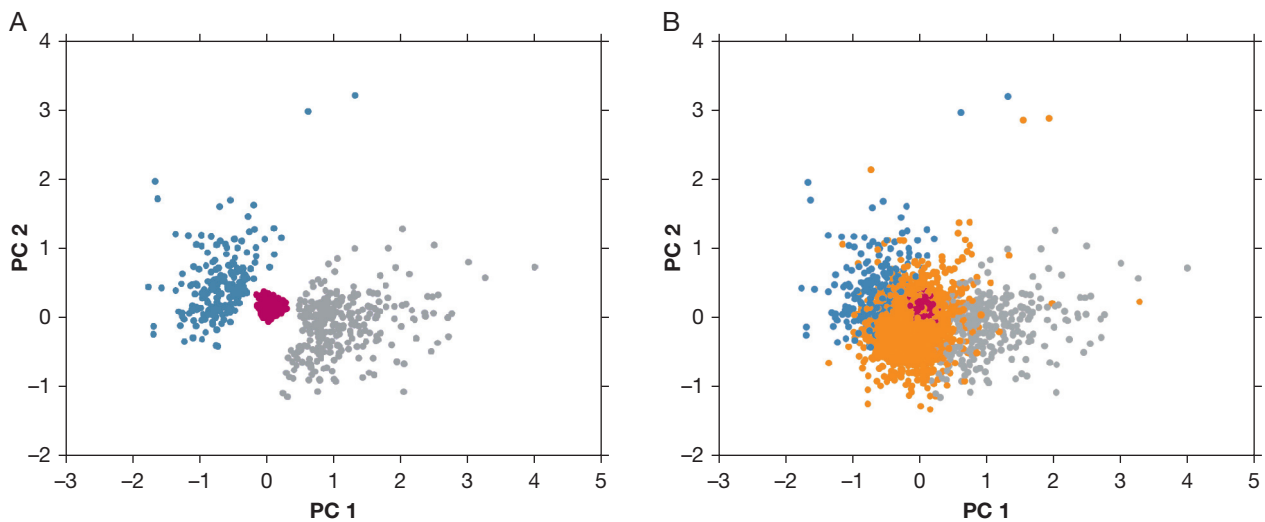


Figure 1 – Principal components analysis (PCA) plot of the residualized lobar emphysema variables. A, The three identified clusters: the minimal emphysema cluster is in red, the upper-lobe-predominant emphysema cluster is in gray, and the lower-lobe-predominant emphysema cluster is in blue. B, The unassigned group is in orange. To summarize the relationships between the five residualized lobar emphysema variables, we performed PCA on these data. The top two principal components (PC) explained almost 80% of the variance in these data (50.7% for PC1 and 26.2% for PC2). PC1 represents an “upper-lobe emphysema axis,” and PC2 is a “lower-lobe emphysema” axis, based on their positive loadings for each kind of emphysema, respectively.

smoking, minimal airway obstruction, more obesity, low comorbidity burden, and mildly impaired health-related quality of life.

#### Five-Year Prospective Change in Imaging

The 5-year changes in imaging measures are shown in Table 2. Over the 5-year follow-up, a more rapid progression of % LAA-950 was observed in subjects with upper-lobe predominance compared with those with lower-lobe predominance (absolute increase of 1.05% vs -0.01%;  $P < .001$ ). The changes in emphysema as a percentage of emphysema at baseline are shown in e-Table 5. Although the absolute increase in emphysema in the group with upper-lobe predominance was modest, the percentage increase in emphysema was notable (emphysema change relative to visit 1, 23% vs -0.1%;  $P < .001$ ), reflecting the fact that roughly half of the group with upper-lobe predominance had  $< 5\%$  emphysema at baseline. These differences in radiological changes remain significant with a consistent direction of effect after accounting for age, sex, race, BMI, pack-years of smoking, change in smoking status between the two visits, and the baseline level of each respective outcome (Table 3). The emphysema distribution pattern remained similar between visit 1 and visit 2 with minimal change noted in the U/L ratio between the two visits for the upper-lobe-predominant and lower-lobe-predominant clusters (Table 2). Since CT emphysema measures were calculated with

implementation of different software at visit 1 and visit 2, Thirona and SLICER % LAA-950 values were compared in 5,000 visit-1 scans processed by both methods, and the correlation was 0.99. A more rapid progression of PRM-emphysema and PRM-fSAD was observed in subjects with upper-lobe predominance compared with those with lower-lobe predominance (absolute change, 0.92% vs 0.04%;  $P < .001$  for PRM-emphysema and 1.56% vs 0.11%,  $P = .01$  for PRM-fSAD) (e-Table 6).

Using stratified analyses, we explored how the relationship between emphysema distribution and emphysema progression is modified by GOLD grade, overall severity of emphysema, BMI, and current smoking. Interestingly, in the lower-lobe cluster, radiological decline was inversely associated with BMI, although the differential associations of upper-lobe clusters vs lower-lobe clusters with total emphysema and emphysema distribution were consistent across BMI strata (e-Table 7). Although more severe in the subjects with total emphysema  $> 5\%$  (e-Table 8), radiological progression was similar at all GOLD grades (e-Table 9). As noted in Table 2, the differences in the % change of gas trapping between visit 1 and visit 2 in the upper-lobe vs lower-lobe clusters had a  $P$  value of .17 in current smokers and .08 in former smokers. The differences in the % change of CT-total lung capacity had a  $P$  value of .16 in current smokers and .02 in former smokers. Conversely, the differences in the % change of total

**TABLE 1 ] Demographic, Imaging, and Clinical Characteristics of the Subjects in Each of the Emphysema Distribution Clusters at Visit 1**

Characteristic	Minimal Emphysema Cluster (n = 1,312)	Upper Lobe-Predominant Cluster (n = 905)	Lower Lobe-Predominant Cluster (n = 796)	P Value (All Groups Omnibus Test)	P Value (Upper-Lobe Predominant vs Lower-Lobe Predominant)
<b>Demographics</b>					
Age, y	53.20 (49.18-59.26)	59.30 (52.50-66.30)	64.00 (57.40-69.83)	< .001	< .001
Male sex, %	36.36	53.37	58.92	< .001	.07
Non-Hispanic whites, %	48.63	61.44	83.67	< .001	< .001
BMI	29.69 (25.91-33.71)	26.64 (23.17-30.33)	28.03 (24.21-32.55)	< .001	< .001
Smoking history (pack-years)	35.80 (24.08-47.10)	43.90 (33.00-61.30)	45.00 (32.68-63.00)	< .001	1.00
Current smoking, %	75.15	57.79	40.83	< .001	< .001
<b>CT measurements</b>					
Total emphysema, % LAA-950)	0.24 (0.14-0.36)	5.44 (2.43-13.76)	5.52 (2.21-16.67)	< .001	.85
U/L ratio	1.08 (0.78-1.51)	4.60 (3.31-7.08)	0.50 (0.39-0.62)	< .001	< .001
Airway wall thickening	61.82 (59.73-64.20)	61.76 (59.49-63.86)	61.48 (59.46-63.91)	.14	.75
Pi10	3.72 (3.66-3.81)	3.68 (3.61-3.76)	3.68 (3.59-3.76)	< .001	.41
Percent gas trapping	4.05 (1.97-8.10)	24.58 (13.80-41.81)	31.30 (12.37-55.29)	< .001	.23
<b>Spirometry</b>					
FEV <sub>1</sub> , % predicted	86.45 (74.80-97.80)	71.70 (52.90-87.00)	65.80 (39.40-86.20)	< .001	< .001
FEV <sub>1</sub> /FVC	0.79 (0.74-0.83)	0.64 (0.51-0.72)	0.59 (0.41-0.74)	< .001	.73
Bronchodilator, % responsiveness (%)	16.86	24.81	27.33	< .001	.78
<b>Symptoms and exacerbations</b>					
MMRC dyspnea score	1.24 ± 1.41	1.67 ± 1.45	1.63 ± 1.45	< .001	1.00
SGRQ score	30.55 ± 25.86	38.65 ± 26.15	36.72 ± 26.80	< .001	.39
Chronic bronchitis, %	17.84	22.65	22.36	.007	1.00
Exacerbation frequency, %	14.94	28.18	28.89	< .001	1.00
<b>Comorbidities, %</b>					
Coronary artery disease	4.50	6.63	10.68	< .001	.01
Diabetes	16.08	10.06	14.82	< .001	.01
Dyslipidemia	35.37	39.34	46.23	< .001	.01
Metabolic syndrome	19.28	13.04	18.84	< .001	.004

(Continued)

**TABLE 1 ] (Continued)**

Characteristic	Minimal Emphysema Cluster (n = 1,312)	Upper Lobe-Predominant Cluster (n = 905)	Lower Lobe-Predominant Cluster (n = 796)	P Value (All Groups Omnibus Test)	P Value (Upper-Lobe Predominant vs Lower-Lobe Predominant)
Obesity	47.64	27.62	35.80	< .001	.001
Sleep apnea	15.10	14.07	22.48	< .001	< .001

Variables are expressed as mean and SD for continuous normally distributed variables, median and interquartile range (25th to 75th percentile) for continuous nonnormally distributed variables, and percentages for categorical variables. Omnibus *P* values are obtained using analysis of variance for the continuous normally distributed variables, the Kruskal-Wallis test for the continuous nonnormally distributed variables, and the  $\chi^2$  test for proportions. *P* values of upper-lobe predominance vs lower-lobe predominance are from pairwise *t* tests, Nemenyi tests, and  $\chi^2$  post hoc tests for pairwise comparisons between upper-lobe-predominant and lower-lobe-predominant clusters for the continuous normally distributed variables, nonnormally distributed variables, and categorical variables, respectively. *P* values < .05 are in bold. Emphysema is defined as percent of CT low-attenuation area < -950 Hounsfield units at end-inspiration using SLICER software. U/L ratio: ratio of % LAA-950 in both upper lobes to that in both lower lobes. Airway wall area percent is the percentage of the wall area compared with the total bronchial area for segmental airways. Exacerbation frequency is the percentage of subjects reporting at least 1 COPD exacerbation in the previous year. Metabolic syndrome = 3 of the following 4: BMI  $\geq$  30 (measured), diabetes mellitus, hypertension, and high cholesterol (all self-reported). Obesity = BMI  $\geq$  30. MMRC = Modified Medical Research Council; % LAA-950 = percent of CT low attenuation area < -950 HU at end-inspiration; Pi10 = square root of the wall area of a hypothetical airway of 10-mm internal perimeter; SGRQ = St. George's Respiratory Questionnaire; U/L ratio = ratio of % LAA-950 in both upper lobes to that in both lower lobes.

emphysema were statistically significant in both current and former smokers.

### Five-Year Prospective Change in Spirometry and Functional Measures

Although suggestive but not nominally significant in univariate analysis (*P* = .10), the association between the group with upper-lobe predominance and an increase in the Modified Medical Research Council (MMRC) score relative to the group with lower-lobe predominance was strongly significant after adjustment for the baseline MMRC score (*P* = .006). No significant differences were detected in multivariate analyses of longitudinal changes of FEV<sub>1</sub> % predicted, 6-min walk distance, or St. George's Respiratory Questionnaire (SGRQ) (Table 3). The statistically significant difference seen in the univariate analysis of FEV<sub>1</sub> (mL/y) was attenuated after adjustment for potential confounders. Stratified analyses suggest that the difference in FEV<sub>1</sub> decline between the group with upper-lobe predominance and the group with lower-lobe predominance is greatest in early GOLD grades (e-Table 8).

### Genome-Wide Association Studies

The quantile-quantile plot of the *P* value distributions and genomic control values demonstrated absence of a systematic inflation (e-Fig 2). No SNPs reached genome-wide significance. However, regions of interest were identified near genome-wide significance, with SNPs at meta-analysis *P* values <  $5 \times 10^{-6}$  (e-Table 10). Nominally significant associations were observed near the *HHIP*, *AGPHD1*, *PPT2/AGER*, *TRAPPC9*, *MYO1D*, *KIAA1462*, and *IREB2/CHRNA3/5* genes (Table 4). Interestingly, for four of the five loci with nominally significant associations with both emphysema distribution subtypes and COPD, the COPD risk allele is associated with upper-lobe predominance.

### Discussion

In this large cohort of smokers without alpha-1-antitrypsin deficiency, random forest clustering identified tightly clustered groups of subjects with distinct cranio-caudal emphysema distribution patterns but similar degrees of total emphysema, measurable airway disease, and cigarette smoking. Compared with lower-lobe-predominant emphysema, subjects with mostly upper-lobe emphysema had less severe lung function impairment and lower rates of obesity and metabolic syndrome at baseline but greater progression of radiological emphysema, gas trapping, and dyspnea after 5 years of follow-up. These two clusters also

**TABLE 2 ] Five-Year Changes in Imaging Characteristics in Upper Lobe-Predominant vs Lower Lobe-Predominant Emphysema Clusters**

Variable	Upper Lobe-Predominant Cluster	Lower Lobe-Predominant Cluster	P Value (Upper-Lobe Predominance vs Lower-Lobe Predominance)
<b>Change of total emphysema (% LAA-950) between visit 1 and visit 2</b>			
All	1.05 (−0.50 to 3.90)	−0.01 (−2.19 to 2.99)	< .001
Current smokers at visit 1 and visit 2	0.95 (−0.25 to 3.18)	−0.17 (−1.40 to 3.20)	< .001
Former smokers at visit 1 and visit 2	0.95 (−0.60 to 3.89)	−0.10 (−3.02 to 2.56)	.003
<b>U/L ratio</b>			
All			
Visit 1	4.09 (2.98 to 7.17)	.65 (.49 to .81)	< .001
Visit 2	3.80 (2.35 to 6.78)	.66 (.46 to .90)	< .001
Current smokers at visit 1 and visit 2			
Visit 1	4.90 (3.38 to 8.09)	.55 (.43 to .69)	< .001
Visit 2	4.40 (2.69 to 8.15)	.51 (.35 to .81)	< .001
Former smokers at visit 1 and visit 2			
Visit 1	3.85 (2.89 to 5.91)	.72 (.55 to .84)	< .001
Visit 2	3.59 (2.21 to 5.85)	.71 (.53 to .91)	< .001
<b>Change of % gas trapping between visit 1 and visit 2</b>			
All	3.66 (−2.79 to 10.50)	1.04 (−4.10 to 6.46)	.001
Current smokers at visit 1 and visit 2	5.97 (0.02 to 12.20)	3.23 (−2.63 to 9.44)	.17
Former smokers at visit 1 and visit 2	2.24 (−4.91 to 7.22)	−0.40 (−4.94 to 3.74)	.08
<b>Change of total lung capacity on CT between visit 1 and visit 2</b>			
All	0.06 (−0.26 to 0.31)	−0.08 (−0.31 to 0.15)	.001
Current smokers at visit 1 and visit 2	0.12 (−0.24 to 0.36)	−0.03 (−0.27 to 0.25)	.16
Former smokers at visit 1 and visit 2	−0.01 (−0.26 to 0.25)	−0.10 (−0.31 to 0.08)	.02

Thirona software was used for % LAA-950. Percent gas trapping was measured at end-exhalation and defined as the percentage of lung voxels with density less than −856 Hounsfield units. Variables are expressed as median and interquartile range (25th to 75th percentile). Change between visit 1 and visit 2 variables is defined as (value at visit 2 − value at visit 1). Negative values indicate decrease of the analyzed variable at visit 2. P values of upper-lobe predominance vs lower-lobe-predominance are from Nemenyi tests for pairwise comparisons between upper-lobe-predominant and lower-lobe-predominant clusters following omnibus Kruskal-Wallis tests. Sample sizes in each subgroup: All (n = 437 [upper-lobe predominance]; n = 394 [lower-lobe predominance]); current smokers at visit 1 and visit 2 (n = 185 [upper-lobe predominance]; n = 102 [lower-lobe predominance]); former smokers at visit 1 and visit 2 (n = 192 [upper-lobe predominance]; n = 222 [lower-lobe predominance]). P values < .05 are in bold. See Table 1 legend for expansion of abbreviations.

demonstrated different patterns of association with established COPD genetic risk variants.

Data mining methods such as cluster analysis enable the identification of discrete groups of patients with similar disease characteristics. These techniques have been previously used in COPD, but no investigation to date has focused on emphysema distribution.<sup>25-27</sup> In a recent study, Castaldi et al<sup>28</sup> directly assessed the reproducibility of different clustering methods applied commonly to COPD clinical variables in 10 independent cohorts of patients with COPD. This analysis revealed that there was higher reproducibility for clustering

methods that excluded individuals who did not clearly belong to any cluster. Based on these novel findings, we selected the random forests clustering approach used for this study precisely because of its ability to discriminate well-clustered from poorly clustered subjects. Thus, our primary goal for this project was not to cluster all subjects with COPD but rather to identify relatively pure subgroups of subjects characterized by upper or lower emphysema predominance. The clustering approach used here was able to identify clearly differentiated upper-lobe-predominant and lower-lobe-predominant emphysema subgroups that had a similar extent of total emphysema, airway disease, and cigarette smoking,



**TABLE 3 ] Multivariate Models of 5-Year Changes in Spirometry, Functional Measures, and Imaging Characteristics in Upper Lobe-Predominant vs Lower Lobe-Predominant Emphysema Clusters**

Upper Lobe-Predominant Cluster vs Lower Lobe-Predominant Cluster	Univariate Model			Multivariate Model 1 <sup>a</sup>			Multivariate Model 2 <sup>b</sup>		
	Beta	SE	P Value	Beta	SE	P Value	Beta	SE	P Value
Change of total emphysema between visit 1 and visit 2, % LAA-950/y	0.19	0.05	<b>&lt; .001</b>	0.14	0.05	0.002	0.15	0.04	<b>&lt; .001</b>
Change of % gas trapping between visit 1 and visit 2, %/y	0.48	0.19	.01	0.47	0.18	0.007	0.50	0.16	.002
Change of FEV <sub>1</sub> between visit 1 and visit 2, mL/y	-9.00	4.62	.05	-3.51	3.78	0.35	-2.57	4.24	.59
Change of FEV <sub>1</sub> between visit 1 and visit 2, % predicted/y	-0.16	0.15	.29	-0.19	0.15	0.23	-0.11	0.14	.42
Change of 6-min walk distance between visit 1 and visit 2, ft	56.00	22.84	.01	22.89	25.73	0.37	-2.03	29.21	.95
Change of SGRQ score between visit 1 and visit 2	-0.42	0.79	.59	0.35	0.97	0.72	0.77	0.95	.42
Change of MMRC dyspnea score between visit 1 and visit 2	0.21	0.13	.10	0.36	0.13	0.008	0.42	0.14	.002

Total emphysema: Percent of CT low attenuation area < -950 Hounsfield units at end-inspiration using Thirona software. Percent gas trapping is measured at end-exhalation and defined as the percentage of lung voxels with density < -856 Hounsfield units. The longitudinal outcomes of change per year for each individual are defined as (value at visit 2 - value at visit 1)/(time between visit 1 and visit 2). Median quantile regression models were used for all the variables except MMRC, in which an ordinal logistic regression model was used. The lower lobe-predominant cluster is the reference cluster. P values < .05 are in bold. MMRC = Modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire. See Table 1 legend for expansion of other abbreviations.

<sup>a</sup>Model 1 includes the following covariates: visit 1 value of the outcome of interest and change in smoking status between visit 1 and visit 2.

<sup>b</sup>Model 2 includes the following covariates: visit 1 value of the outcome of interest, change in smoking status between visit 1 and visit 2, age, sex, race, BMI, and pack-years of smoking. Change in smoking status between visit 1 and visit 2 was defined as: "Current to former smoker", "former to current smoker", "current; unchanged", or "former, unchanged".

enabling the further characterization of these specific subgroups. These subgroups would not have been identified with the more traditional approach of thresholding based on differences or ratios in the percentages of emphysema in upper vs lower lobes.

Our findings are consistent with prior reports of more severe airway obstruction in lower zone-predominant emphysema and are reflective of the dominant contribution of the lower lobes to the forced expired maneuver.<sup>29-32</sup> Since most of these studies included more advanced stages of COPD, our observations extend those findings to subjects with mild to moderate COPD. Investigating 115 smokers with mild to moderate COPD (58 of whom had emphysema), de Torres et al<sup>33</sup> did not demonstrate any significant association between craniocaudal emphysema distribution and lung function parameters, likely because of the smaller sample size and the differences in the methods of assessing emphysema distribution compared with our study.

To our knowledge, this is the first report of an association between an upper-lobe emphysema subtype and faster rates of overall emphysema progression. In a cohort of 587 male smokers followed for 3 years, a faster

spirometric decline was observed in upper-lobe emphysema compared with lower-lobe emphysema, but emphysema progression was not assessed.<sup>34</sup> Our study also demonstrated an association between upper-lobe emphysema and more rapid disease progression, but our significant findings were primarily limited to emphysema progression. Although we did observe a significant univariate association demonstrating more rapid decline in FEV<sub>1</sub> (mL/y) in the group with upper-lobe predominance, this association was no longer significant after adjustment for baseline FEV<sub>1</sub>. Bhatt et al<sup>14</sup> showed that decline in FEV<sub>1</sub> in mild to moderate disease is associated with airway disease and emphysema, and in our study, the upper-lobe and lower-lobe clusters had similar degrees of measurable airway disease and overall emphysema, potentially explaining the lack of significant difference in FEV<sub>1</sub> decline between the two clusters.

Diabetes and the metabolic syndrome are frequent comorbidities in patients with COPD. These comorbidities have been shown to be more frequent in airway-predominant COPD,<sup>35,36</sup> and this study extends those results to subjects with lower lobe-predominant

**TABLE 4 ]** Associations With Known COPD Susceptibility or Emphysema Distribution Genetic Variants, or Both, Comparing the Upper Lobe-Predominant Cluster and the Lower Lobe-Predominant Cluster

Candidate SNP	Locus	Nearest Gene	Effect Allele	Effect Allele Frequency in Non-Hispanic Whites	Effect Allele Frequency in African Americans	Meta-analysis GWAS: Upper Lobe vs Lower-Lobe Clusters <sup>a</sup>			GWAS: COPD Cases vs Control Subjects <sup>b</sup>		
						OR	SE	P Value	Case-Control OR	Case-Control SE	Case-control P Value
rs13141641	4q31	<i>HHIP</i>	T	0.61	0.91	1.45	1.09	<b>1.20 × 10<sup>-5</sup></b>	1.27	1.03	<b>4.6 × 10<sup>-13</sup></b>
rs9788721	15q25	<i>AGPHD1</i>	T	0.60	0.61	0.78	1.08	<b>.0009</b>	0.79	1.03	<b>5.2 × 10<sup>-13</sup></b>
rs12914385	15q25	<i>IREB2/CHRNA3/5</i>	T	0.41	0.19	1.30	1.08	<b>.0009</b>	1.29	1.03	<b>2.1 × 10<sup>-15</sup></b>
rs75755010	8q24	<i>TRAPPC9</i>	A	0.95	0.88	0.66	1.18	<b>.009</b>	1.01	1.07	.86
rs2070600	6p22	<i>PPT2/AGER</i>	T	0.04	NA	1.77	1.25	<b>.01</b>	0.71	0.08	<b>2.9 × 10<sup>-5</sup></b>
rs35374984	10p12	<i>KIAA1462</i>	A	0.88	0.47	1.29	1.11	<b>.02</b>	1.11	1.05	<b>.02</b>
rs379123	17q11	<i>MYOID</i>	T	0.41	0.34	0.85	1.08	<b>.03</b>	0.94	1.03	.05
rs2645694	4q13	<i>SOWAHB</i>	T	0.74	0.58	1.17	1.09	.07	1.00	1.04	.9
rs7957346	12q22	<i>SNRPF</i>	A	0.56	0.60	0.88	1.08	.08	1.08	1.03	<b>.02</b>
rs7733088	5q32	<i>HTR4</i>	A	0.40	0.32	0.88	1.07	.08	0.91	1.03	<b>.004</b>
rs754388	14q32	<i>RIN3</i>	C	0.82	0.86	1.19	1.11	.09	1.29	1.04	<b>1.5 × 10<sup>-9</sup></b>
rs75200691	8p22	<i>DLC1</i>	T	0.88	0.92	0.82	1.13	.1	1.05	1.05	.34
rs7698250	4p15	<i>DHX15</i>	T	NA	0.94	0.66	1.40	.21	0.94	0.15	.67
rs56113850	19q13	<i>CYP2A6/ADCK4</i>	T	0.61	0.55	0.88	1.11	.23	0.8	1.04	<b>1.1 × 10<sup>-7</sup></b>
rs7221059	17q25	<i>MGAT5B</i>	A	0.81	0.69	0.90	1.10	.27	1.02	1.04	.64
rs9590614	13q14	<i>VWA8</i>	C	0.60	0.85	0.95	1.08	.49	1.02	1.03	.5
rs2234922	1q41	<i>EPHX1</i>	A	0.19	0.33	1.05	1.09	.56	0.96	1.04	.26
rs626750	11q22	<i>MMP12</i>	A	0.82	0.73	1.05	1.10	.61	0.83	1.04	<b>2.9 × 10<sup>-6</sup></b>
rs10411619	19p13	<i>MAN2B</i>	T	0.01	0.21	1.08	1.18	.64	0.96	1.08	.58
rs10844154	12p11	<i>BICD1</i>	A	0.44	0.43	1.03	1.08	.65	1.02	1.03	.5
rs2250889	20q13	<i>MMP9</i>	C	0.04	0.16	1.06	1.16	.68	1.00	1.06	.97
rs4846480	1q41	<i>TGFB2</i>	A	0.75	0.67	1.03	1.08	.68	1.17	1.03	<b>5.6 × 10<sup>-6</sup></b>
rs4416442	4q22	<i>FAM13A</i>	T	0.58	0.46	0.98	1.08	.76	0.79	1.03	<b>3.5 × 10<sup>-14</sup></b>
rs45505795	14q32	<i>SERPINA10</i>	C	0.96	0.99	1.05	1.25	.84	1.52	1.11	<b>3.4 × 10<sup>-5</sup></b>
rs9478940	6q25	<i>GSTP1</i>	A	0.83	0.41	1.00	1.10	.96	1.04	1.04	.28

A total of 25 SNPs were considered in this analysis. They were selected on the basis of previously published genome-wide significant associations with COPD case-control status, qualitative or quantitative CT measurements of emphysema, and emphysema distribution. The analyses were adjusted for pack-years of smoking, current smoking, genetic ancestry, and sex. OR was calculated with the upper-lobe predominant cluster as the reference group in the upper-lobe vs lower-lobe GWAS, and COPD cases were the reference group in the case-control GWAS. P values < .05 are bold. GWAS = genome-wide association study; NA = not available; SNP = single nucleotide polymorphism.

<sup>a</sup>The present study.

<sup>b</sup>The published GWAS of COPD case-control status.<sup>18</sup>

emphysema. These comorbidities are all related to systemic inflammation, which may explain the co-occurrence. It is also possible that this is a reflection of worse lower-lobe mechanics leading to more immobility, obesity, and associated cardiovascular disease.

In our prior GWAS of emphysema distribution,<sup>8</sup> we identified five loci associated with continuous emphysema distribution measures at genome-wide significance. In this current study, we sought to supplement these findings by determining the genetic associations in distinct groups of subjects with upper-lobe-predominant vs lower-lobe-predominant emphysema, but we did not identify any novel genome-wide significant associations, likely because this analysis was limited to a subset of subjects from the overall cohort and therefore had less power to detect genetic associations. In addition to the top GWAS signals, we chose to also report the associations with SNPs already known to be associated with COPD or emphysema, since these SNPs are already of interest to the study of COPD and its related phenotypes. Although the number of nominally significant associations in this set of known COPD/emphysema variants suggests that genome-wide significant associations may be identified with a larger sample size, these non-genome-wide significant associations should be interpreted cautiously.

One of the interesting findings from this analysis is the observed higher prevalence of the COPD risk allele in subjects with upper-lobe predominance that suggests a potential link between upper-lobe predominance and common risk variants for COPD. As suggested by the pathway analyses that we reported in our previous publication,<sup>8</sup> emphysema distribution shares some of the processes that occur in general COPD pathogenesis and progression, but other pathways may be specific to the pathogenesis of emphysema distribution. The precise reasons for the upper-lobe predominance in smokers without alpha-1-antitrypsin deficiency and emphysema are unclear, but it has been attributed to regional differences in perfusion, transit time of leukocytes, clearance of deposited dust, mechanical stress, and pleural pressure.<sup>20,24,37,38</sup> It is also noteworthy that in this current manuscript, we analyzed common genetic

variants only (ie, variants with major allele frequency > 1%) and had limited power to detect small effect sizes. We therefore cannot exclude the possibility that rare genetic variants or common variants with smaller effect sizes, or both, are involved and have differential associations with COPD susceptibility and emphysema distribution.

Our study has a number of strengths. It is the first study designed to identify emphysema distribution subtypes using data-driven methods, and it is the largest analysis to date of emphysema distribution in well-characterized smokers with a wide range of COPD disease severity and longitudinal follow-up data. In addition, the lobar segmentation approach used to generate our emphysema measures was shown to provide improved characterization of emphysema distribution compared with nonanatomic approaches.<sup>39</sup>

This study has several limitations. First, we focused exclusively on craniocaudal emphysema distribution variables. However, other measures of emphysema distribution have been described in the literature, such as core-rind and centrilobular/panlobular/paraseptal distributions<sup>40</sup> and warrant future explorations. Second, unsupervised clustering is an exploratory analysis method, and the generalizability of these results to other cohorts cannot be assumed. Third, BMI has a strong inverse association with total emphysema<sup>14,30,40</sup> and may also confound emphysema measures due to technical artifact induced by scatter effects.<sup>41,42</sup> However, apicobasal emphysema is effectively standardized within the same subject, making this measure more likely to be robust to technical artifacts than is total emphysema.<sup>41</sup> In addition, most of our observed associations remained significant after adjusting for BMI.

In conclusion, this cluster analysis using lobar emphysema identifies subgroups of smokers that differ by craniocaudal emphysema distribution patterns, disease progression, and genetic associations. These findings may be of importance in optimizing participant selection in future clinical trials to ultimately improve and personalize therapy.

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**Additional information:** The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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