Familial aggregation of FEF25–75 and FEF25–75/FVC in families with severe, early onset COPD

D L DeMeo, V J Carey, H A Chapman, J J Reilly, L C Ginns, F E Speizer, S T Weiss, E K Silverman

Background: The Boston Early-Onset COPD study showed that current or ex-smoking first degree relatives of severe early onset COPD probands have significantly lower forced expiratory volume in 1 second (FEV1) and FEV1/forced vital capacity (FVC) values than current or ex-smoking control subjects, which suggests the existence of genetic risk factors for the development of COPD in response to cigarette smoking. We hypothesised that first degree relatives of early onset COPD probands may also have lower values of spirometric parameters such as forced expiratory flow at the mid-portion of forced vital capacity (FEF25–75) and FEF25–75/FVC.

Methods: Using generalised estimating equations, FEF25–75 and FEF25–75/FVC were analysed in 333 first degree relatives of probands with severe early onset COPD and 83 population based controls; analyses were also performed on data stratified by smoking status. Narrow sense heritability estimates were calculated using a variance component approach.

Results: Significantly lower FEF25–75 and FEF25–75/FVC were observed in smoking (FEF25–75: β = −0.788 l/s (95% CI −1.118 to −0.457), FEF25–75/FVC: β = −20.4% (95% CI −29.3 to −11.6, p = 0.0001 for both phenotypes) and non-smoking (FEF25–75: β = −0.357 l/s (95% CI −0.673 to −0.041, p = 0.0271), FEF25–75/FVC: β = −9.5% (95% CI −17.1 to −1.9, p = 0.0145)) first degree relatives of early onset COPD probands. Narrow sense heritability estimates for FEF25–75 (h² = 0.38) and FEF25–75/FVC (h² = 0.43) were similar to those for FEV1 and FEV1/FVC.

Conclusion: Lower values of FEF25–75 and FEF25–75/FVC in non-smoking first degree relatives of early onset COPD probands than in controls suggest a genetic susceptibility to develop obstructive lung disease, independent of smoking, which is magnified by exposure to deleterious environments as suggested by the further decrements in FEF25–75 and FEF25–75/FVC seen in smoking first degree relatives. FEF25–75 and FEF25–75/FVC have high heritability and are important intermediate phenotypes for inclusion in genetic epidemiological studies of COPD.
Pulmonary function testing

Spirometric tests were performed for first degree relatives and control subjects with a Survey Tach spirometer (Warren E Collins, Braintree, MA, USA) as previously described. The manoeuvres were performed in accordance with ATS criteria, with all subjects seated and wearing nose clips. Participants were asked to desist from using inhaled bronchodilators for 4 hours before testing, if possible. The values presented for FEV₁ represent the highest value for any effort, and FEV₁/FVC, FEF₂₅–₇₅ and FEF₂₅–₇₅/FVC represent values from the best test effort, defined as the manoeuvre with the highest sum of FEV₁ plus FVC. Height was measured in stocking feet. Percentage predicted values were calculated using prediction equations as defined by Hankinson and colleagues. Pre- and post-bronchodilator (180 μg albuterol) spirometry was performed.

Statistical methods

All computations were performed with the SAS statistical package (SAS Statistical Institute, Cary, NC) on a SUN server running the UNIX operating system. The Student’s t test was used to compare the mean values between first degree relatives and controls for unadjusted and percentage predicted pulmonary function parameters. Unadjusted values for pulmonary function parameters were considered in multivariate regression models that included age, age², sex, height, height², race, and pack years of smoking. As a number of individuals were included from each early onset COPD family and each control family, generalised estimating equation (GEE) models were used for regression. GEE models account for the positive correlation between family members within a familial cluster. Since age is an important contributor to pulmonary function outcomes, regression analyses were performed on the overall group of participants and a subset that excluded individuals 18 years or younger. Heritability estimates were computed using all individuals from the early onset COPD pedigrees. Narrow sense heritability estimates (h²) were calculated using a variance component approach in the SOLAR program; this estimate represents a ratio of the phenotypic variance due to additive genetic effects divided by the total trait phenotypic variance. The heritability estimates were calculated with inclusion of age, sex, race, height, pack years of cigarettes, pack years², age², and height² as covariates.

RESULTS

Demographic and spirometric data of first degree relatives stratified by smoking status

As previously reported, the probands with early onset COPD had severe airflow obstruction (mean FEV₁ among probands of 16.1% predicted for men and 17.5% predicted for women). Most of the early onset COPD probands were female

| Table 1 Baseline demographic and pulmonary data stratified by smoking status |
|------------------|------------------|------------------|------------------|------------------|
|                  | Non-smokers      | Smokers          |                  |
|                  | First degree     | Controls (n = 35) | First degree     | Controls (n = 48) | p value |
|                  | relatives (n = 132) |                  | relatives (n = 201) |                  |
| F/M              | 83/49            | 18/17            | 102/99           | 29/19            | 0.290 |
| Mean (range) age* | 35.2 (7.8–80.0) | 39.9 (19.5–84.3) | 45.8 (15.1–87.0) | 48.6 (18.5–83.4) | 0.020 |
| Race (white/black) | 126/6            | 35/0             | 200/1            | 48/0             | 0.050 |
| Pack years smoking† | 0               | 0               | 28.1 (25.3)      | 22.1 (22.1)      | 0.132 |
| FEV₁ (% predicted) | 93.90 (12.51)   | 93.81 (13.24)    | 76.74 (22.67)    | 89.21 (14.42)    | <0.0001 |
| FVC (% predicted)  | 99.70 (11.26)   | 96.44 (13.54)    | 88.31 (17.51)    | 92.02 (9.94)     | 0.053 |
| FEV₁/FVC†         | 77.98 (7.32)    | 78.78 (6.97)     | 68.38 (14.07)    | 76.76 (8.55)     | <0.0001 |
| FEF₂₅–₇₅ (% predicted) | 76.02 (24.52) | 82.99 (26.33)    | 54.70 (29.96)    | 77.90 (35.27)    | <0.0001 |
| FEF₂₅–₇₅/FVC†     | 72.05 (24.12)   | 77.15 (24.01)    | 51.58 (27.30)    | 70.34 (26.91)    | <0.0001 |

*When 22 non-smoking and two smoking first degree relatives aged 18 years or younger were removed from the analysis the means and age ranges were 39.9 (18.3–80.0) for non-smokers and 46.1 (18.1–87.0) for smokers. These values were not statistically different from controls (p = 0.884 for non-smokers, p = 0.340 for smokers).

†Values are mean (SD).
Among the smokers, despite similar ages and mean pack years of smoking, first degree relatives had lower mean percentage predicted FEV₁ and FEF₂₅–₇₅ values; among the smokers the unadjusted values (not shown) for FEV₁/FVC, FEF₂₅–₇₅ and FEF₂₅–₇₅/FVC were also significantly lower in first degree relatives of early onset COPD probands. No significant differences in the mean values for unadjusted or percentage predicted FEV₁, FVC, FEV₁/FVC, FEF₂₅–₇₅, or FEF₂₅–₇₅/FVC values were seen in non-smoking first degree relatives compared with controls (not shown), although there was a trend towards lower values of FEF₂₅–₇₅ percentage predicted and FEF₂₅–₇₅/FVC in first degree relatives of early onset COPD probands. When individuals aged 18 years or younger were removed, percentage predicted FEF₂₅–₇₅ and FEF₂₅–₇₅/FVC were significantly lower in first degree relatives than controls. Frequency histograms for FEF₂₅–₇₅ for smoking and non-smoking first degree relatives and controls demonstrate these trends (fig 1).

### Multivariate regression models for pulmonary function outcomes

To assess familial aggregation of FEF₂₅–₇₅ and FEF₂₅–₇₅/FVC in smokers, multivariate regression was performed using the unadjusted spirometric values in GEE models which included the usual covariates for which pulmonary function measures are adjusted (height, age, race, sex). When multivariate models were analysed with pulmonary function phenotypes as continuous outcomes in all subjects (not stratified by smoking status), first degree relatives of early onset COPD probands had lower values than controls for FEV₁, FEF₂₅–₇₅, and FEF₂₅–₇₅/FVC (table 2); there was no significant difference for adjusted FVC. In current or former cigarette smokers there were also statistically significant decrements in FEV₁, FEF₂₅–₇₅, and FEF₂₅–₇₅/FVC among the first degree relatives (table 2). Inclusion of current smoking status in the model did not alter the trend of these findings (data not shown). In non-smokers there were no differences between first degree relatives and controls for FEV₁ and FVC. However, FEF₂₅–₇₅ and FEF₂₅–₇₅/FVC were significantly reduced among non-smoking first degree relatives compared with non-smoking controls (table 2). Residual analysis confirmed the robust nature of these findings (data not shown).

22 non-smokers and two smokers aged 18 years or younger resulted in more comparable age ranges between the first degree relatives and controls.

![Cumulative frequency histograms for FEF25–75 percentage predicted in (A) current and ex-smoking first degree relatives of severe early onset COPD probands and controls and (B) non-smoking first degree relatives of severe early onset COPD probands and controls. (A) Approximately 59% of first degree relatives had percentage predicted FEF25–75 of less than 80% compared with 35% for controls. (B) Approximately 55% of first degree relatives had percentage predicted FEF25–75 less than 80% predicted compared with 48% for controls.](http://www.thoraxjnl.com)

### Table 2: Multivariate regression models for predicting pulmonary function in all subjects and after excluding those aged 18 years or younger

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>All‡</th>
<th>Non-smokers§</th>
<th>Smokers¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (l)</td>
<td>–0.214 (–0.334 to –0.093)</td>
<td>0.0005</td>
<td>–0.048 (–0.194 to 0.098)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>–0.019 (–0.152 to 0.114)</td>
<td>0.7749</td>
<td>0.079 (0.076 to 0.233)</td>
</tr>
<tr>
<td>FEF₂₅–₇₅ (l/s)</td>
<td>–0.605 (–0.855 to –0.356)</td>
<td>&lt;0.0001</td>
<td>–0.357 (–0.673 to –0.041)</td>
</tr>
<tr>
<td>FEF₂₅–₇₅/FVC (%)</td>
<td>–0.3499 (–0.528 to –0.172)</td>
<td>0.0001</td>
<td>–0.294 (–0.501 to –0.088)</td>
</tr>
<tr>
<td>FEF₂₅–₇₅/FVC (%)</td>
<td>–1.51 (–2.15 to –0.87)</td>
<td>0.0001</td>
<td>–9.5 (–17.1 to –1.9)</td>
</tr>
<tr>
<td>FEF₂₅–₇₅/FVC (%)</td>
<td>–11.2 (–17.1 to –5.2)</td>
<td>0.0002</td>
<td>–8.7 (–15.5 to –2.0)</td>
</tr>
</tbody>
</table>

*Beta values presented are the regression coefficients for first degree relatives with controls as the reference group with confidence intervals in parentheses.
†Model includes FEV₁.
‡Age, age², height, height², sex, race, and pack years in model.
§Excluding subjects aged 18 years and younger.
¶Model includes FEV₁.
the setting of an appropriate environmental exposure. of a susceptibility to develop clinically significant disease in
strong genetic control, as well as being potentially indicative
first degree relatives. Identification of phenotypic character-
FEV1/FVC. The current investigation of first degree relatives
FEV1 and FEV1/FVC compared with control subjects of
the same age and smoking history. 8 No increased risk for
phenotypic expression due to gene
under genetic influence and subject to modification of
environmental factors. The only known genetic
risk factor for COPD is severe α1-antitrypsin deficiency, and
research efforts are ongoing in an attempt to localise the
other genetic influences on this complex disease. From an
environmental perspective, cigarette smoke exposure is an
established risk factor. Probands with severe early onset
COPD were culled in an effort to define other genetic factors
in the analysis. The heritability estimates for FEF25–75 and
FEF25–75/FVC were at least equal to those values for FEV1 and
FEV1/FVC, with narrow sense heritability estimates for
FEF25–75 and for FEF25–75/FVC calculated as 0.38 and 0.45,
respectively.

Heritability of spirometric phenotypes
Heritability estimates were obtained for 576 individuals in
the Boston Early-Onset COPD Study pedigrees for all
spirometric parameters (table 3). Proband and all extended
family members who participated in this study were included
in the analysis. The heritability estimates for FEF25–75 and
FEF25–75/FVC were at least equal to those values for FEV1 and
FEV1/FVC, with narrow sense heritability estimates for
FEF25–75 and for FEF25–75/FVC calculated as 0.38 and 0.45,
respectively.

**DISCUSSION**
The phenotypic expression of COPD is under both genetic and
environmental influence. As a complex human disease,
COPD is heterogeneous in presentation, with variable severity
and anatomical distribution. To date, the only known genetic
risk factor for COPD is severe α1-antitrypsin deficiency, and
research efforts are ongoing in an attempt to localise the
other genetic influences on this complex disease. From an
environmental perspective, cigarette smoke exposure is an
established risk factor. Probands with severe early onset
COPD were culled in an effort to define other genetic factors
relevant to the heritability and expression of COPD. This
cohort of individuals with severe early onset COPD has
disease out of proportion to age and smoking histories,
suggesting the presence of an underlying susceptibility that is
under genetic influence and subject to modification of
phenotypic expression due to gene × environment inter-
actions. Familial aggregation has previously been reported for
COPD and for spirometric measures of pulmonary function.
Most of the earlier investigations have focused on FEV1 and
FEV1/FVC. The current investigation of first degree relatives
of early onset COPD probands provides further insight into
the familial aggregation of spirometric phenotypes. A previous analysis of spirometric phenotypes in the first 44
degree relatives of this early onset COPD cohort showed that
current and ex-smoking first degree relatives had reduced
FEV1 and FEV1/FVC compared with control subjects of
similar age and smoking history. 6 No increased risk for
decrements in FEV1, or FEV1/FVC was seen in non-smoking
first degree relatives. Identification of phenotypic character-
istics that differentiate non-smokers is important as this may
point to intermediate phenotypes of COPD that are under
strong genetic control, as well as being potentially indicative
of a susceptibility to develop clinically significant disease in
the setting of an appropriate environmental exposure.

This current analysis in the Boston Early-Onset COPD Study extends the previous analysis to the flow related
measures FEF25–75 and FEF25–75/FVC, and identifies these
flow parameters as potential indicators of genetic suscept-
bility to develop COPD. Cohen et al10 have suggested familial
ggregation of phenotypes related to abnormalities in forced
expiration, finding differences in Vmax for lifetime non-
smokers together with decrements in Vmax, V50, and V25
flow related measures among first degree relatives who smoke. 11 Our findings are potentially suggestive of a
heritable abnormality in airways development that may
predispose to disease susceptibility later in life. Since these
decrements are manifest in non-smokers and are of a larger
magnitude in first degree relatives who smoke, our results
suggest both a baseline genetic predisposition for lower
FEF25–75 and FEF25–75/FVC as well as a potential genetic ×
smoking interaction that accentuates the decrements in
FEF25–75 and FEF25–75/FVC. These findings remained robust
after the exclusion of individuals with low FEV1, suggesting
that the observations in smokers and non-smokers are not
being driven by individuals who already have low lung
function. There was no change in the findings of lower
spirometric measures among the smoking first degree
relatives compared with controls, regardless of how smoking
was considered as a covariate (current smoking, ever
smoking, pack years smoked). This suggests that differential
inflammatory effects of current smoking at the time of
spirometry are not the explanation for our results. This study
did not quantify the amount of childhood exposure to smoke
experienced by first degree relatives; assessment of childhood
smoke exposure is subject to potential recall bias. Adding
childhood tobacco smoke exposure as a yes/no variable to our
multivariate models did not change the results among the
smokers or non-smokers.

Our analysis has several important limitations. The Boston
Early-Onset COPD Study cohort is predominantly white, so
generisability of these findings to individuals and families
of other races may be limited. The rate of recruitment among
the controls was low; only 20 control probands and 83 total
controls were recruited from letters sent out to individuals
who had been previous participants in population based
studies from our laboratory. 9 The size of the control group is
an important consideration as we interpret our findings, and
a larger control group would strengthen the interpretability
and generalisability of our results. Despite the potentially
increased measurement related variability in FEF25–75 and
FEF25–75/FVC, the fact that there was any difference between
the non-smokers suggests that these phenotypes are impor-
tant to consider in genetic epidemiology studies, even if the
absolute magnitude of our findings may be influenced by the
small size of our control group. The sensitivity analyses
performed by removing the younger individuals suggest that
our results are not being driven by a small number of younger
individuals in the early onset COPD pedigrees. FEF25–75 is a
more variable measure than FEV1, but the same technique
and spirometric equipment were used to measure this
parameter in all subjects, which may contribute to increased
accuracy of measurement of these phenotypes. Lastly, we do
not have longitudinal follow up data to assess the develop-
ment of COPD in the first degree relatives, nor do we have
radiographic correlates assessing the presence of emphysema
in the first degree relatives or controls. Longitudinal
investigation and confirmation of these findings in an
independent cohort is a goal of future studies.

Abnormalities in FEF25–75 have been considered as
evidence for small airways disease, 12 although other investi-
gators have suggested that this measure does not provide
information beyond FEV1/FVC for characterising small air-
way disease. 13–21 Alternatively, decrements in FEF25–75/FVC
may represent variations in lung elastic recoil or other
acquired/inherited abnormalities in airway function, vari-
bility in genetically programmed responses to oxidative and

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**Table 3** Heritability estimates for spirometric parameters

<table>
<thead>
<tr>
<th>Spirometric parameter</th>
<th>Mean (SE) h²</th>
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<tbody>
<tr>
<td>FEV1</td>
<td>0.32 (0.06)</td>
</tr>
<tr>
<td>FVC</td>
<td>0.31 (0.06)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.31 (0.05)</td>
</tr>
<tr>
<td>FEF25–75</td>
<td>0.38 (0.10)</td>
</tr>
<tr>
<td>FEF25–75/FVC</td>
<td>0.45 (0.09)</td>
</tr>
</tbody>
</table>

*Age, sex, race, height, pack years of cigarettes, age², height², and pack years included as covariates in the model.

**n = 583 individuals.**

**n = 576 individuals.**
proteolytic stress in the lungs, or may be the result of airway/ 
lung parenchyma dysanapsis. FEF25–75/FVC has been used as 
as a measure of dysanaptic lung growth, the physiologically 
normal but non-isotopic lung growth that occurs between 
the airways and lung parenchyma. Tager and colleagues have 
shown that FEF25–75/FVC is highly correlated with Mead’s 
earlier measures of dysanapsis (as measured by the ratio of 
maximal flow at 50% vital capacity × static recoil pressure of 
the lung at 50% vital capacity).22 23 Dysanaptic lung growth 
may predispose to the development of obstructive lung 
disease24 25 and may also predict airway hyperresponsiveness.26 
Chen and colleagues27 have recently investigated 
whether dysanaptic lung growth has a genetic component.27 
They investigated Vmax50/FVC using segregation analysis 
and suggested that dysanaptic growth of the lung airways to 
parenchyma is under major gene control.

Although we do not currently have longitudinal follow up 
data on the first degree relatives of early onset COPD 
probands to assess the development of lung disease, it is 
our hypothesis that the first degree relatives of individuals 
with severe early onset disease who demonstrate reduced 
levels of spirometric flow parameters have increased suscept-
ity to develop airflow obstruction later in life. The decrements of FEF25–75 and FEF25–75/FVC in non-smoking 
first degree relatives suggest a phenotypic difference from 
population based controls. This finding may be related to a 
baseline susceptibility to develop lung disease in families of 
probands with early onset COPD, with an increased risk to 
develop airflow obstruction in the setting of gene × 
environment (smoking) interactions. Importantly, we have 
shown significant heritability estimates for FEF25–75 and 
FEF25–75/FVC similar to those for FEV1 and FEV1/FVC. These 
findings suggest the importance of including these additional 
spirometric measures as intermediate phenotypes in studies of 
the genetic epidemiology of COPD.

In summary, investigation of the spirometric character-
istics of first degree relatives of probands with severe early 
onset COPD unrelated to severe α1-antitrypsin deficiency 
dined reductions in FEF25–75 and FEF25–75/FVC in smoking 
and non-smoking first degree relatives, with heritability 
estimates that are comparable to FEV1 and FEV1/FVC. These 
findings suggest that genetic factors may be relevant to the 
determination of FEF25–75 and FEF25–75/FVC. Since differ-
ences between non-smokers have not been demonstrated in 
our cohort for FEV1 and FEV1/FVC, this suggests that FEF25– 
75 and FEF25–75/FVC may represent genetic effects that are 
manifest early in life and identify a disease susceptibility 
characteristic that is highly heritable. FEF25–75 and FEF25–75/ 
FVC are important intermediate phenotypes to consider in 
genetic linkage and association studies of COPD.

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