

# Progress in disease progression genetics: dissecting the genetic origins of lung function decline in COPD

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Lung function is a heritable trait. Heritability estimates posit that approximately 30%–50% of the phenotypic variation in FEV<sub>1</sub> is explained by genetics,<sup>1–3</sup> and genome-wide association studies (GWAS) of lung function<sup>4–11</sup> have discovered multiple genetic variants that are associated with cross-sectional measurements in adults of FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC ratio at genome-wide significance levels. Many of these same loci have also been implicated in GWAS of COPD. Additional work is required to link these loci to pathophysiology. Functional studies on GWAS loci involving *HHIP*<sup>12</sup>, *FAM13A*,<sup>14</sup> *HTR4*,<sup>15</sup> *AGER*<sup>16</sup> and *IREB2*<sup>17</sup> have already provided important insights into the biological mechanisms for genetic determinants of COPD and/or lung function.

Longitudinal change in lung function ( $\Delta$ FEV<sub>1</sub>,  $\Delta$ FEV<sub>1</sub>/FVC) is also heritable,<sup>18</sup> albeit perhaps to a lesser degree than cross-sectional lung function levels. Although studies of longitudinal lung function have discovered a few loci associated with  $\Delta$ FEV<sub>1</sub> at genome-wide significance levels, none were robust to replication in the available populations. While at first glance the genetic determinants of FEV<sub>1</sub> level and  $\Delta$ FEV<sub>1</sub> might be expected to show significant overlap, a recent study of COPD by Lange *et al*<sup>19</sup> and a complementary study in asthma by McGeachie *et al*<sup>20</sup> have suggested that low maximum attained lung function and accelerated lung function decline are distinct processes that can exert independent effects on the risk for chronic airflow obstruction. Therefore, it would not be surprising if different genetic determinants influenced cross-sectional and longitudinal lung function change. Longitudinal measurements of lung function are highly informative for identifying

these separate processes. In contrast, one cannot distinguish between subjects with low maximum attained lung function and decline in cross-sectional studies of middle-aged to older adults in whom airways obstruction has already developed.

Dr John *et al*<sup>21</sup> focused on two questions of interest for lung function and COPD research: First, can we identify novel genetic determinants of longitudinal lung function decline? Second, are genetic determinants of cross-sectional lung function related to longitudinal changes in lung function?

To investigate the first question, John *et al* conducted a two-stage GWAS of longitudinal lung function measures (FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC) including 4167 subjects of European ancestry from the Busselton Health Study with, on average, three spirometric measurements spanning 15 years. The initial stage of the analysis yielded 45 regions of interest with association p value  $<5 \times 10^{-6}$  for longitudinal FEV<sub>1</sub> decline, FVC decline or FEV<sub>1</sub>/FVC decline (including two regions associated with longitudinal decline in FEV<sub>1</sub> that met a genome-wide significance threshold of  $5 \times 10^{-8}$ ), which were followed up in the Lung Health Study and Copenhagen City Heart Study cohorts. These associations with longitudinal lung function were not replicated, similar to previous publications.<sup>22–23</sup>

The second question was addressed by assessing the aggregate effect of previously identified cross-sectional lung function GWAS variants on longitudinal change in FEV<sub>1</sub> and FEV<sub>1</sub>/FVC using a genetic risk score. The genetic risk score composed of variants associated with cross-sectional lung function showed a strong association with cross-sectional lung function levels, demonstrating the validity of previously published associations of these variants with lung function levels in their cohort; however, the score showed no significant relationship to longitudinal lung function measures. The authors propose that cross-sectional lung function variants may exert their effects in determining initial lung development and maximum lung function, rather than in determining rates of subsequent lung function decline.

This study was limited by sample size in comparison to recently published GWAS of cross-sectional lung function and COPD. Other limitations of the study included spirometric measurements that were not standardised throughout the entire study period, tobacco smoking not adjusted for in the primary model and assessment of a single genetic ancestry group. Despite these limitations, these data are thought-provoking for the pathogenesis of lung function decline and progression to obstructive lung disease.

Studying genetic determinants of longitudinal change in lung function is challenging, because assessment of longitudinal change involves phenotypes that are likely noisier than cross-sectional measurements. Noise in longitudinal measurements can occur through changes in measurement technique, variability in the number of measurements per subject and a subject's variability in performance during testing. With a small number of measurements per subject, estimation of change over time in a phenotype of interest is hindered by measurement variability in the level of that phenotype at each time point; while data from this study spanned almost 40 years, some subjects had only two spirometric measurements while others had up to eight measurements. The assessment of rate of decline in lung function based on eight data points is likely much more reliable than that based on two points. In addition, in COPD, rates of  $\Delta$ FEV<sub>1</sub> appear to slow as the disease progresses,<sup>24–25</sup> survivor effects may limit the assessment of subjects with high rates of decline and progression may not follow a linear trajectory due to episodic decline from exacerbations or other acute events.

In the two largest studies of longitudinal lung function to date, replication of genetic associations has been elusive. There are many potential reasons for this lack of replication. The simple phenotype of  $\Delta$ FEV<sub>1</sub> may not provide optimal power to detect what may be a diverse group of genetically determined pathways of lung function decline. Variability in  $\Delta$ FEV<sub>1</sub> could occur through many different mechanisms including differences in disease activity, response to tobacco smoking or air pollution and the subject's immune response to injury and infection. Thus, accurate subtyping of subjects with COPD may be a promising approach to increase our power to detect associations in the datasets available today. The genetic drivers of lung function decline may also be influenced by gene-by-environment interactions. Examples of these environmental factors could include heterogeneous exposures like tobacco

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smoke, outdoor environmental exposures that might differ on an urban/rural axis like particulate matter or reactive oxygen species, or even regional exposures such as ambient humidity and temperature.

Because of these factors, substantially larger sample sizes will likely be required to identify genetic determinants of longitudinal lung function. Whether the determinants of maximum attained lung function and longitudinal rate of lung function decline are genetically distinct, or whether larger studies will discover broader genetic connections between cross-sectional and longitudinal lung function, remains to be seen. However, it is worthwhile to pursue these goals, since identifying novel genes and functional variants can point to key biological pathways and help to differentiate genetic determinants of maximum attained lung function and rates of lung function decline in the general population from disease-specific genetic determinants of COPD.

Although studies of COPD progression have traditionally relied on changes in lung function, the growing availability of CT imaging-based assessments of emphysema and airway disease provides additional opportunities for assessing COPD progression—and genetic studies of longitudinal imaging phenotypes are an important future direction. Imaging phenotypes and integrative omics assessments of gene expression, proteomics and metabolomics may assist in the identification of subjects with greatest COPD disease activity and disease progression for clinical trials as well as for genetic studies.

Larger GWAS meta-analyses of lung function and COPD continue to discover additional genetic associations with cross-sectional data, and a subset of these associated regions may still reveal important insight into longitudinal lung function in larger studies. However, we need more longitudinal studies of lung function and other phenotypes—both in general populations and disease-specific cohorts—to help determine genetic drivers of COPD progression. This study and the studies by Hansel *et al* and Tang *et al* represent an important contribution in respiratory genetics towards investigating genetic mechanisms of disease through longitudinal phenotyping. Identifying subjects with a higher genetic risk for rapid lung

function decline will likely improve prediction of COPD risk, advance prognostication of COPD outcomes and provide a pool of common and rare genetic markers that may lead to actionable protein targets and disease mechanisms.

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