Systemic Biomarkers of Lung Function and FEV1 Decline Across Multiple Cohorts

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Rationale: Chronic obstructive pulmonary disease (COPD) is a common respiratory disease that is characterized by airway obstruction and accelerated lung function decline. However, our understanding of systemic markers of COPD remains incomplete. Objectives: We tested whether aptamer-based protein profiling could identify markers and pathways associated with impaired pulmonary function and lung function decline in multiple studies. Methods: We studied 3,827 non-Hispanic and European White participants across four population-based cohorts and two longitudinal COPD case-control studies with both aptamer-based plasma proteomic data on 1,305 proteins and spirometry measurements. In linear regression models we examined protein associations with baseline FEV_1 (Liters) and FEV_1/FVC (ratio). Models for FEV1 adjusted for age, age2, height, height 2, sex, body mass index (BMI), smoking status, pack-years smoking. Models for FEV_1/FVC ratio were adjusted for age, sex, BMI, smoking status, pack-years, and COPD case status in COPDGene and SPIROMICS (defined as FEV_1/FVC < 0.7). In linear mixed effects models we investigated the association of baseline protein levels with rate of lung function decline (FEV_1 ml/year) in 2,636 participants across four cohorts. The model included a random intercept and fixed effects for time, protein and its interaction with time, baseline age, gender, height, baseline smoking status and pack-years. Benjamini-Hotchberg adjusted false discovery rate Q-value<0.05 was used to determine statistical significance. Measurements and Main Results: We identified 198 proteins associated with baseline FEV_1, among which 12 proteins were also significantly associated with FEV_1/FVC. Novel associations include retinal binding protein 4 (FEV_1: β= 0.0307; $Q=2.18\times10^{-4}$ and FEV_1/FVC: β= 0.008; $Q=4.00\times10^{-3}$) and bactericidal permeability increasing protein (FEV_1: β=-0.0280; $Q=6.80\times10^{-3}$ and FEV_1/FVC: β=-0.005; Q=0.047). We identified 15 proteins associated with the rate of FEV_1 decline (Q< 0.05), many of which were novel including tissue factor, the coagulation cascade initiator (β= -5.21 ml/year; 95% CI, -7.82 to -2.61; Q= 0.016), nidogen, an extracellular matrix protein (β=-4.90 ml/year; 95% CI,-7.45 to -2.36; Q=0.020) and angiogenin, a potent angiogenic factor (β=-6.42; 95% CI, -9.71 to -3.14; $Q=2.18\times10^{-4}$). Pathways associated with lung function included extracellular matrix remodeling, dysregulation of coagulation and angiogenesis. Conclusions: In this study, we have identified many novel circulating protein associations with baseline lung function and FEV_1 decline. These associations could represent novel molecular targets and pathways to modify the clinical course of COPD or be used for preventive and therapeutic strategies.

This abstract is funded by: COPDGene Phase 3. U01 HL089897 and U01 HL089856. COPD Foundation (AstraZeneca, Boehringer-Ingelheim, Genentech, GlaxoSmithKline, Novartis, Sunovion). FHS: R01HL132320 and R01HL133870, NO1-HC-25195, HHSN268201500001I and 75N92019D00031. KORA: German Federal Ministry of Education and Research , State of Bavaria. LMUinnovativ, German Center for Lung Research. LSC: State of New Mexico. MESA-TOPMed/MESA Lung Study: 3R01HL-120393-02S1; HHSN268201800001I. HHSN2682015000031/HHSN26800004). R01-HL077612 and R01-HL093081. SPIROMICS: HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, HHSN268200900020C, U01 HL137880 and U24 HL141762, Foundation for the NIH and COPD Foundation (AstraZeneca; Bayer, Bellerophon, Boehringer-Ingelheim, Chiesi Farmaceutici, Forest Research, GlaxoSmithKline, Grifols, Ikaria, Novartis, Nycomed GmbH, ProterixBio, Regeneron, Sanofi, Sunovion, Takeda, Theravance Biopharma, Mylan).

Am J Respir Crit Care Med 2020;201:A5527
Internet address: www.atsjournals.org **Online Abstracts Issue**