Proteomics of CT Emphysema Subtypes in the General Population. The Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study

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Chronic obstructive pulmonary disease (COPD) and pulmonary emphysema were the third-leading cause of death globally in 2019. Besides alpha-1 antitrypsin deficiency, emphysema lacks disease-modifying medications due to its heterogeneity and there remains a need to further investigate emphysema subtypes to advance its diagnosis and treatment. Recent unsupervised machine learning of the texture and anatomical location of emphysema on computed tomography (CT) images of the lung defined six quantitative CT emphysema subtypes uniquely associated with specific gene variants, environmental exposures, symptoms, physiology and clinical events.
We aim to identify associations of plasma proteins with each CT emphysema subtype cross-sectionally in a multi-ethnic general population sample.
MESA is a prospective cohort study that recruited 6,814 participants from six communities who self-identified as White, Black, Hispanic, or Asian race/ethnicity, ages 45-84 years old and free of clinical cardiovascular disease in 2000-02. The MESA Lung Study performed CT scans among 3,137 participants in 2010-12, which were labeled with previously described (PMID: 37268414) CT emphysema subtypes. Proteomics was assessed using SomaScan version 4.1 assay (7,596 plasma proteins). Linear regression models were adjusted for age, height, weight, sex, race, educational attainment, smoking status, pack years, urine cotinine level, body-mass index (BMI), estimated glomerular filtration rate (eGFR), CT scanner manufacturer and other CT emphysema subtypes. Results were adjusted to reflect a False Discovery Rate (FDR) p-value of less than 5% using the Benjamini-Hochberg method.
Among 2,343 participants with both CT and proteomic data (mean age 69.5 years, 52.3% women, 23.7% with COPD), we identified statistically significant associations of proteins with the vanishing lung subtype (42 proteins; top hit Natural cytotoxicity triggering receptor 3 ligand 1, $q = 2.9*10^{-9}$), restrictive combined pulmonary fibrosis/emphysema (CPFE) subtype (11 proteins; top hit Integrin alpha-2/b1, $q=1.0*10^{-5}$), the combined bronchitis-apical emphysema subtype (9 proteins; top hit

Desmoglein-2, q=8.8*10^{-13}), and the diffuse emphysema subtype (4 proteins; top hit Pulmonary surfactant-associated protein D, q=5.7*10^{-3}). No significant proteins were associated with the obstructive CPFE or senile subtypes after FDR correction. Most proteins were uniquely associated with one CT emphysema subtype, while a few proteins were associated with more than one subtype.
This study identified specific proteins for different CT emphysema subtypes, many of which have been related less specifically to emphysema, including pulmonary surfactant production, anti-inflammatory pathways, and mitochondrial deregulation, amongst others. Validation of these proteomic associations can provide insight into further pathway assessment, clinical biomarker discovery, and targeted prevention of emphysema in the general population.

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