TMF: Constructing and Evaluating Omic Risk Scores for Chronic Obstructive Pulmonary Disease Prediction and Classification

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Abstract: Penalized regression models leveraging human genotype data to construct polygenic risk scores (PRSs) have been shown to stratify individuals for risk of many complex diseases, and high-risk individuals can be targeted for more aggressive screening, preventive treatment, and other interventions. Unfortunately, PRSs often display limited predictive power. Recently, groups have extended PRS approaches to ‘omics data to develop ‘omics risk scores (ORSs) and disease risk models incorporating ORSs in addition to PRSs have been observed to have improved precision when predicting disease. Despite rapid advancement of ORSs, there has yet to be a comparison of their performance across different ‘omics data and trait architectures.

In this TOPMed Fellowship application, I propose to integrate ‘omics data from the Genetic Epidemiology of COPD (COPDGene) study to construct ORSs of COPD and related traits (including spirometric and computed tomography (CT) measures, multiple severity scores, exacerbations, and additional clinical measurements). While this approach could be applied to a variety of TOPMed traits, I will focus this study on chronic obstructive pulmonary disease (COPD), which is a complex trait and the sixth leading cause of death in the United States [1]. COPD is an inflammatory disease characterized by airway obstruction with multiple clinical phenotypes and variable progression. There are multiple disease trajectories, with patients presenting with varying levels of airway obstruction and emphysema (destruction of distal airspaces), with specific molecular signatures and pathways in smokers who develop airflow obstruction, emphysema, or no lung disease. My aims are to (1) build methylation (MRS), transcriptome (TRS), metabolomic (MetRS), and proteomic (ProtRS) risk scores for COPD and related traits in the COPDGene study; (2) evaluate the predictive performance of ORSs relative to and combined with PRSs and relevant clinical factors, phenotypic variance explained by ORSs, and evidence of confounding by demographic factors; and (3) validate ORSs in two independent TOPMed cohorts: SPIROMICS (Study of COPD Subgroups and Biomarkers) and MESA (MultiEthnic Study of Atherosclerosis).

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