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PROJECT SUMMARY/ABSTRACT
The interstitial lung diseases (ILDs) are characterized by alveolar injury, inflammation, and fibrosis. Idiopathic pulmonary fibrosis (IPF), the most common and deadly fibrotic ILD, affects up to 100,000 Americans. The search for an effective therapy for lung fibrosis has been elusive and may require identification and investigation of an earlier stage of the disease, prior to the onset of irreversible lung fibrosis. Unfortunately, most affected individuals present with advanced lung fibrosis, hampering efforts to understand the early events leading to ILD. We recently identified subclinical ILD using a CT-based phenotype (high attenuation areas, HAA) in the Multi-Ethnic Study of Atherosclerosis (MESA), an NHLBI-funded population-based cohort of 6,814 participants age 45-84 years of European, African, Hispanic, and Chinese descent who underwent longitudinal cardiac CT scanning between 2000 and 2007. CT scans are being repeated in 2010-12. We have performed preliminary studies in MESA and the Columbia IPF Study suggesting that elevated HAA is novel imaging biomarker of subclinical ILD. We now propose to perform additional studies to demonstrate that the biology and physiology of elevated HAA resembles that of clinical ILD. We also propose to perform genome-wide linkage and association studies of elevated HAA. Therefore, we will (a) measure HAA in the remaining MESA cardiac CT scans performed between 2002 and 2012 to establish a longitudinal case definition of subclinical ILD, (b) measure serum levels of SP-A, SP-D, MMP-1, and MMP-7 in 581 cross-sectional cases and 493 longitudinal cases of subclinical ILD and a comparison group of 1,200 MESA participants, and (c) measure resting and exercise lung function in 100 MESA participants. We propose to use these new data and existing genetic linkage and association data from the MESA, MESA Family, and MESA SHARe studies to accomplish three Specific Aims: Specific Aim 1: To determine if cases with elevated HAA have higher serum levels of markers of AE C injury (SP-A and SP-D) and ECM remodeling (MMP-1 and MMP-7) compared to a comparison group. Specific Aim 2: To test the hypothesis in MESA participants that individuals with elevated HAA have impaired lung function compared to those with normal HAA. Specific Aim 3: To perform statistical genetic analyses of quantitative (HAA) and qualitative (elevated HAA) phenotypes of subclinical ILD in the MESA and MESA Family studies. If we achieve our Aims, our proposed study will establish elevated HAA as a novel CT-based biomarker of ILD to be used in future studies of the molecular and genetic basis of ILD. Our genetics Aim is designed to provide new data to stimulate additional research into the mechanisms of early ILD pathogenesis with the potential to discover novel pathways and therapeutic targets to prevent lung fibrosis.