Genetic variants associated with bronchodilator responsiveness

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A new study from Brigham and Women's Hospital (BWH) reveals several new gene variants that are associated with how people living with chronic obstructive pulmonary disease (COPD) respond to inhaled bronchodilators. COPD is a progressive breathing disorder that limits airflow in the lungs. Bronchodilators are medicines used to alleviate respiratory disorder symptoms.

The abstract for this meta-analysis study will be presented at the American Society of Human Genetics 2013 meeting, Oct. 22 to 26 in Boston.

One of the research goals was to identify single nucleotide polymorphisms (SNPs) associated with bronchodilator responsiveness (BDR).

"Identifying single nucleotide polymorphisms associated with bronchodilator responsiveness may reveal genetic pathways associated with the pathogenesis of COPD and may identify novel treatment methods," said Megan Hardin, MD, BWH Channing Division of Network Medicine, lead study author.

The researchers used statistical methods to combine results from 5,789 Caucasian patients with moderate to severe COPD from four individual studies. The genotypes of over 700 African Americans with COPD were also analyzed.

Most (4,561) of the patients in the four cohorts studied had over 10 pack-years of smoking. The group whose members had greater than 5 pack-years of smoking totaled 364, and the cohort with greater than two and one-half years totaled 864.

All patients were genotyped, and their lung function was tested by spirometry before and after they used the bronchodilator medication albuterol, which relaxes muscles in the airways and increases air flow to the lungs. Spirometry measures the volume and flow of air that is exhaled.

The researchers investigated over 6.3 million unique SNPs from the patients' genotypes. They discovered four novel variants that rarely occur in the general population.

According to Hardin, there may be multiple genetic determinants that likely influence bronchodilator responsiveness. The researchers caution that more extensive functional analysis of the SNPs will be required.

"As we continue to analyze the data, we expect to identify other important SNPs," said Craig P. Hersh, MD, BWH Channing Division of Network Medicine, senior study author.

Each patient's bronchodilator responsiveness (BDR) was determined by three measures: absolute change in the volume of air exhaled during a forced breath in one second (FEV1) (BDRABS); change as percentage of predicted FEV1 (BDRPRED); and change as percentage of baseline FEV1 (BDRBASE).

The researchers reported that the top SNPs thus far have been associated with each BDR outcome, but emphasized that additional analysis may reveal other SNPs with equally or greater influence on COPD patients' response.

The meta-analysis revealed the top SNPs for each BDR outcome:

SNPs in the:

- HS6ST3 gene were associated with BDRBASE
- XKR4 gene were associated with BDRPRED and BDRBASE
- CUBN gene were associated with BDRABS and BDRPRED

Among African American participants, SNPs in the CDH13 gene were significantly associated with BDRABS.

The cohorts included in the meta-analysis were: ECLIPSE (1,764 patients) and COPDGene (2,797 patients), all of whom had over 10 pack-years of cigarette smoking; NETT (364 patients) with over five pack-years smoking; and GenKOLs (864 patients with over 2.5 pack-years of smoking).

Provided by Brigham and Women's Hospital