Gene Variant Deemed Protective of the Lungs

BY MARY ANN MOON

A variation in the MMP12 gene appears to be associated with beneficial pulmonary effects in children who have asthma and in adults who smoke, particularly smokers with chronic obstructive pulmonary disease, according to a study.

"Our results suggest that variants of MMP12 are determinants of the level of lung function in subjects who are at risk for airflow obstruction," said Dr. Gary M. Hunninghake and Dr. Michael H. Cho of Brigham and Women's Hospital, Boston, and their associates.

The investigators tested for an association between single-nucleotide polymorphisms (SNPs) in the MMP12 gene and lung function as assessed by forced expiratory volume in 1 second (FEV_1) in cohorts participating in seven clinical trials. The MMP12 gene encodes matrix metalloproteinase 12, which is produced by macrophages, "the predominant cell type that patrols the lower airspaces under normal conditions and the main inflammatory cell type that is recruited with smoking," the investigators noted.

Matrix metalloproteinases degrade extracellular matrix molecules such as collagen and elastin and are also involved in epithelial repair and the regulation of cytokine and chemokine activity.

The researchers first found that the minor allele of SNP rs2276109 in the MMP12 gene was significantly associated with increased FEV_1 in children with asthma (but not nonasthmatic children) who were subjects in the Genetics of Asthma in Costa Rica Study. They then found the same link between the SNP and increased FEV_1 among children taking budesonide—but not among those who were not taking budesonide—in the Childhood Asthma Management Program. The same link between the SNP and increased FEV_1 existed among children with asthma (but not nonasthmatic children) in the BAMSE (Children, Allergy, Milieu, Stockholm, Epidemiological Survey) study.

Dr. Hunninghake and his colleagues then tested for the same association in adults who were subjects in the Boston Early-Onset COPD Study, the Lovelace Smokers Cohort, and the Normative Aging Study. The researchers found that the same SNP variation was associated with improved lung function in adults who were current or former smokers, but not in nonsmokers.

Finally, the investigators found that the same MMP12 variant appeared to protect patients at risk for COPD against the disease in those same three adult cohorts. The absence of the SNP rs2276109 was associated with a 54% increase in the risk of the onset of COPD and a population attributable risk of COPD of 28%.

The findings support the so-called "Dutch hypothesis," which states that asthma and COPD are different manifestations of a single disease entity and suggests that as-yet unknown genetic variants may underlie both asthma and COPD, the investigators said (N. Engl. J. Med. 2009;361[doi:10.1056/NEJMoa0904006]).

Most previous studies of genetic associations in pulmonary function have relied on a single cohort, the study's authors noted. "A strength of our study is that it included the analysis of multiple measurements of pulmonary function in a large number of subjects—more than 20,000 FEV_1 measurements in more than 8,300 subjects," they added.

"Evidence is accumulating that asthma and COPD share common pathogenetic pathways," noted Dr. Guy G. Brusselle of Ghent (Belgium) University Hospital, in an accompanying editorial. "This study … adds to the accumulating evidence that several mechanisms may lead to the development of COPD" (N. Engl. J. Med. 2009;361[doi:10.1056/NEJMe0919626]).

The study's strengths include the inclusion of seven cohorts with more than 8,300 subjects; the replication of an association between the SNP and FEV_1 both in adult smokers and children with asthma; and the researchers' ability to repeat the analyses after stratification for asthma status and smoking status.

Dr. Hunninghake and Dr. Cho reported no conflicts of interest. Their associates reported receiving support from a several pharmaceutical companies. ■