Genetic irregularities linked to higher risk of COPD among smokers

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Scientists at Duke University Medical Center have discovered two genetic markers that appear to put some smokers at significantly higher risk of developing chronic obstructive pulmonary disease (COPD).

The findings come from the first-ever genome-wide association study of COPD and suggest that those who carry the markers may be able to reduce their risk if they quit smoking before the first symptoms of COPD occur.

"The public health message would probably be 'quit before it's too late,'" says David Goldstein, Ph.D., director of the Institute for Genome Sciences Center for Human Genome Variation at Duke and the senior author of the study appearing in *PLoS Genetics*.

Chronic obstructive pulmonary disease is one of the leading causes of death worldwide. While smoking is the biggest risk factor, there is considerable variation among those who develop the disease. Genetics plays a role, but until now, there has only been one biological marker proven to be associated with COPD - a deficit of the protein A1AT, which has also been linked to the development of lung cancer.

"But we know that A1AT deficiency appears in only 1-2 percent of people with COPD, so we were pretty sure that there had to be other genetic variants at work, as well," says Goldstein.

To discover if that hunch might prove true, Goldstein led an

international team of investigators in examining the genomes of 823 people with COPD and 810 smokers without COPD in Norway. They were looking for the presence of the 100 top genetic variations already documented in individuals with COPD enrolled in the family-based International COPD Genetics Network. They then took the most frequently occurring alterations from that study and evaluated them in three additional, independent groups: patients in the U.S. National Emphysema Treatment Trial, individuals enrolled in the Boston Early-Onset COPD study and a control group from the Normative Aging Study.

The genome-wide association study revealed several genetic aberrations that might be linked to COPD. But after a series of statistical analyses, only two single letter changes in DNA - (called single nucleotide polymorphisms, SNPs, or "snips") emerged as significant. Both were located near a nicotine receptor on chromosome 15 that has already been associated with lung cancer and other respiratory disorders. The SNPs also appeared with significant frequency among members of the international COPD genetics and emphysema groups.

"We believe that smokers who have these two SNPs face a nearly two-fold increase in risk of developing COPD, when compared with those who do not have these gene variants," says Goldstein. "We also believe that these two alterations directly affect how the lungs function - that they may actually mediate the risk of developing COPD."

The authors also ran tests among those who developed COPD and those who did not to find out if there was any relationship between the variants and how much people smoked. They didn't find any association, reinforcing the notion that these variants influence risk independent of smoking behavior.

The findings represent the discovery of the first major locus contributing

to COPD in the general population. While Goldstein says the discovery may well open new therapeutic windows, it may also prompt clinicians to take another look at how they assess health risk among smokers.

"While it is clear that choosing to smoke is one of the worst health decisions a person can make, we now know that choice is even worse for some people than others," Goldstein said. "Our study also suggests that familiar measures of risk such as packs per day or smoking years, while informative, tell only a part of the story. The rest of the story is all about genetics, and it is still being written."

Source: Duke University Medical Center