Genetic variations raise lung cancer risk for smokers and ex-smokers

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Two common inherited genetic variations are associated with increased risk of lung cancer for smokers and former smokers, a research team led by scientists at The University of Texas M. D. Anderson Cancer Center reports April 2 in the online edition of *Nature Genetics*.

"This is the first study to identify a common genetic variant that influences the risk for developing lung cancer," said lead author Chris Amos, Ph.D., professor in M. D. Anderson's Department of Epidemiology. The variants are present in about half of the Caucasian population studied.

The paper is one of three published by Nature this week from three unique teams that have identified the same genetic locus as associated with increased lung cancer risk. The findings are a major step forward in identifying those at high risk for non-small cell lung cancer and for understanding how smoking and genetic factors interact to cause the disease.

"The major risk factor for developing lung cancer is cigarette smoking," Amos said. "What we do not understand is why some long-term smokers develop lung cancer and others don't. There are so many different cancer-causing compounds in tobacco smoke that it's hard to separate them and we don't fully understand the mechanisms that cause lung cancer."

While all smokers and former smokers are at higher risk for lung cancer, less than 20 percent of these "ever smokers" eventually develop the

disease. "We need to get a better handle on how genetic factors increase risk and what molecular pathways are involved in development of lung cancer," Amos said.

The research team, comprising scientists from M. D. Anderson, Johns Hopkins University, and the Institute for Cancer Research and the University of Cambridge in the United Kingdom, pinpointed two spots of genetic variation on chromosome 15.

The two variants are single-nucleotide polymorphisms (SNPs, pronounced "snips"), places in the human genome that vary by a single DNA chemical building block or nucleotide. Individuals who have ever smoked and who have one or two copies of either of these SNPs have increased risks ranging from 28 percent to 81 percent of developing lung cancer, the researchers found.

The team's findings might also provide support for a growing body of evidence suggesting that nicotine, long known as the prime addictive compound in cigarettes, might also play a direct causative role in the development of lung cancer.

There are five genes in the area of chromosome 15 where the two risk-raising SNPs were identified, Amos explained. Of those, three are nicotine acetylcholine receptor genes that encode proteins that serve as docking sites to which nicotine can bind.

"Once bound, these receptors set in motion a cascade of signals. Nicotine is known to activate cell proliferation, new blood vessel development and growth factors while upregulating several signaling pathways. If these are indeed causal genes, that will be of great interest," Amos said.

Another potential causative gene in the area is one that encodes a

component of the proteasome, which degrades other proteins. The function of the fifth gene has yet to be identified.

Further studies with additional SNPs in African-American populations who show different SNP patterns may help to define which of these five genes causes lung cancer. Collaborations with both M. D. Anderson's Lung SPORE and the Kleberg Center for Molecular Markers will evaluate whether these SNPs influence expression of any of these five genes in lung cancers and normal lung tissue, Amos said.

Lung cancer causes more deaths than any other cancer, killing more than 160,000 Americans annually and millions worldwide. Non-small cell lung cancer makes up 80 percent of all lung cancer cases.

Amos and senior co-author Margaret Spitz, M.D., chair of M. D. Anderson's Department of Epidemiology, conceived the study, which follows on evidence from epidemiological research indicating a two-fold increase in lung cancer risk for first-degree relatives of lung cancer patients.

To pinpoint genetic variations, the team conducted a series of genome-wide association studies, first genotyping 317,498 different SNPs among 1,154 former and current smokers who developed lung cancer and were seen at M. D. Anderson and 1,137 matched ever-smoker controls in Houston.

This first phase of the study narrowed the search to 10 SNPs, which were then genotyped in 711 additional cases and 632 controls from the same Houston population to identify the final two SNPs. A second replication phase was conducted among 2,013 ever-smoker lung cancer cases and 3,062 controls in the United Kingdom.

To minimize confounding from risk factors and to increase the study's

ability to pinpoint genetic effects, controls were matched to lung cancer cases according to smoking behavior, age and sex. Former smokers were matched by years since they stopped smoking. The study was performed first in Caucasians to minimize the effect of ethnic genetic variation.

The team carefully analyzed its findings to exclude the possibility that the elevated risk from the two SNPs was attributable to their association with heavier smoking. "Our study shows a weak effect (of these two SNPs) on smoking behaviors and an extremely significant effect on lung cancer risk, whether or not adjustment for smoking behavior is made during the analysis," the authors conclude.

The genetic variations might help identify smokers at higher lung cancer risk who would be the best candidates for screening. And they may be useful to gauge the risk of other smoking-related cancers, such as esophageal, bladder, head and neck, and pancreatic cancer. A similar genome-wide study of African-American smokers is planned.

Research was funded principally by the National Cancer Institute of the National Institutes of Health. Lung cancer patients and controls for the Texas components of the study came from a long-term, 17-year study of the epidemiology of lung cancer at M. D. Anderson, which was funded by the National Cancer Institute and led by Spitz.

"We are very indebted to the patients who have participated in the study," Spitz said. "There is no immediate benefit to the patients themselves, but they willingly agree to participate in our research and their help has been invaluable. Being able to conduct this analysis should be useful to future generations who develop lung cancer."

Source: University of Texas M. D. Anderson Cancer Center