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### **Location of Potential Familial Lung Cancer Gene Discovered**

Researchers have discovered a possible inherited component for lung cancer, a disease normally associated with external causes, such as cigarette smoking. An interdisciplinary consortium consisting of 12 research institutions and universities, including the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both part of the National Institutes of Health (NIH), identified a major lung cancer susceptibility region on a segment of chromosome 6. The findings appear in a just-posted-online edition of *American Journal of Human Genetics*\* and will appear in print in the September 2004 issue.

The Genetic Epidemiology of Lung Cancer Consortium (GELCC) \*\* examined 52 families who had at least three first-degree family members affected by lung, throat, or laryngeal cancer. Of these 52 families, 36 had affected members in at least two generations. Using 392 known genetic markers, which are DNA sequences that are known to be common sites of genetic variation, the researchers generated and then compared the alleles (the different variations each gene can take) of all affected and non-affected family members who were willing to participate in the study.

The researchers found strong evidence that a lung cancer susceptibility gene or genes is co-inherited with a genetic marker on chromosome 6. Markers on chromosomes 12, 14, and 20 also indicated possible linkage to lung cancer susceptibility, although the results were not as strong. Identifying the locus was a critical first step, but more work needs to be done.

“The genetic markers are like those mileage markers you see on the side of the highway,” explained NCI’s Jonathon Wiest, Ph.D. “They can be very useful for broad navigational purposes, but at the same time they don’t give you precise information about all the interesting things that may lie along the highway.”

The next goal for these researchers is to more closely examine this region of chromosome 6 with the aim of locating the exact gene or genes that cause lung cancer susceptibility. The identified region corresponds to roughly a 20 million base pair segment on the long arm of chromosome 6. The region contains numerous genes that are likely candidates for the susceptibility gene, including four suspected tumor suppressor genes. However, Wiest pointed out that “often you can discover a new function for a gene that normally works in a different cellular pathway, so you never know what you’re going to find.”

Another interesting discovery the team made involved the effects of smoking on cancer risk for carriers and non-carriers of the predicted familial lung cancer gene. They found that in non-carriers, the more they smoked, the greater their risk of cancer. In carriers, on the other hand, any amount of smoking increased lung cancer risk. These findings suggest that smoking even a small amount can lead to cancer for individuals with inherited susceptibility.

The researchers also plan to continue screening additional families who could have familial lung cancer, to confirm this particular susceptibility region, and perhaps find additional regions. “The discovery of genes for other types of cancer has led to better understanding of those diseases, which in turn can lead to better strategies for treatment and prevention. We hope that uncovering a gene or genes responsible for lung cancer will do the same for this devastating disease,” said co-lead author Joan Bailey-Wilson, Ph.D., NHGRI.

Lung cancer is by far the leading cause of cancer death in the United States (over 160,000 deaths expected in 2004), and the five-year survival rate is only 15 percent. Such a high mortality, combined with the large amount of spontaneous lung cancers that arise from smoking, makes finding potential histories of familial lung cancer or collecting genetic samples extremely difficult and time consuming. “This study is just further proof of the importance of cooperative efforts and large-scale science in genetic epidemiology research,” said Daniela Seminara, Ph.D., NCI.

NHGRI and NCI are two of the 27 institutes and centers at NIH, an agency of the Department of Health and Human Services.

For more information about cancer, visit the NCI Web site at <http://www.cancer.gov> or call NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237).

Additional information about NHGRI can be found at its Web site, [www.genome.gov](http://www.genome.gov).

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\* Bailey-Wilson JE, Amos CI, Pinney SM, Petersen GM, de Andrade M, Wiest JS, Fain P, Schwartz AG, You M, Franklin W, Klein C, Gazdar A, Rothschild H, Mandal D, Coons T, Slusser J, Lee J, Gaba C, Kupert E, Perez A, Zhou X, Zeng D, Liu Q, Zhang Q, Seminara D, Minna J, Anderson M. A major lung cancer susceptibility locus maps to chromosome 6q23-25. *American Journal of Human Genetics*, September 2004.

\*\* The Genetic Epidemiology of Lung Cancer Consortium (GELCC) includes Jonathon Wiest, Ph.D., and Daniela Seminara, Ph.D., both of NCI; Joan Bailey-Wilson, Ph.D., of NHGRI; Christopher Amos, Ph.D., of M.D. Anderson Cancer Center; Gloria Petersen, Ph.D., and Mariza de Andrade, Ph.D., of the Mayo Clinic; Susan M. Pinney, Ph.D., of the University of Cincinnati; Pamela Fain, Ph.D., of the University of Colorado Health Sciences Center at Denver; Ann Schwartz, Ph.D., of Karmanos Cancer Institute; Ming You, M.D., Ph.D., of Washington University (St. Louis); Adi Gazdar, M.D., and John Minna, M.D., of University of Texas Southwestern Medical Center; Henry Rothschild, M.D., of Louisiana State University Health Sciences Center at Dallas; and Teresa Coons, Ph.D., of the Saccomanno Research Institute. The GELCC is headed by Marshall Anderson, Ph.D., of the University of Cincinnati.