

## Lung Cancer Genetics: A Family Affair?

□□ Commentary on You et al., p. 2666

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Lung cancer risk has a genetic component. This study reports the discovery of a gene variant that is overexpressed in patients who have the familial, but not sporadic, type of lung cancer. This report provides new insights into a mechanism that will help to guide preventive interventions in the future.

In this issue of *Clinical Cancer Research*, You and colleagues (1) present the results of a family-based study of lung cancer, the Genetic Epidemiology of Lung Cancer Consortium (GELCC). This study represents a significant contribution to our understanding of lung cancer susceptibility and is another step toward the goal of preventive medicine.

There are several significant challenges to understanding variation in an individual's or a population's susceptibility to an environmentally induced disease such as lung cancer. Firstly, the genetic landscape of human susceptibility is complex. There are likely to be only rare instances in which mutations within a single gene convey significant sensitivity to typical levels of exposure. More likely, there will be many genes with moderate or small effects, which, in combination, result in disease susceptibility after carcinogen exposure. Gene-environment interactions, as well as interactions among genetic variants (gene-gene interactions), and epigenetic processes, are likely to play a significant role in determining disease susceptibility to an exposure, either by altering the biological effective dose to the lung (Fig. 1), or by altering the linear exposure-response relationship. Moreover, although tobacco smoking results in the majority of lung cancer in the world, there are many other causes of lung cancer, such as exposures to asbestos, arsenic, radon products, air pollution, etc. Also, in East Asia, the majority of women who develop lung cancer neither smoke nor have occupational exposures to known lung carcinogens, raising the possibility of exposure to other things, such as viruses. This etiologic heterogeneity presents methodologic challenges for research, and hence for prevention and control.

Secondly, we are only beginning to understand the distribution of single-nucleotide polymorphisms (SNPs) in the human genome and to type large numbers of SNPs accurately. Ideally, we would like to measure all known SNPs in epidemiologic or clinical studies, eliminating the puzzle of whether unmeasured genetic variants contribute to observed variation in disease risk or progression. Currently, in population genetics, multistaged

research strategies, such as linkage analysis to identify potential genomic regions, followed by positional candidate gene studies, or genomic scans with tag SNPs, followed by fine mapping, are employed to identify a set of genes and their variants that are most significantly associated with disease susceptibility. These multistaged approaches typically assume that individual mutations have statistically significant and context-independent (i.e., some disease association in different populations or other contexts) disease associations. However, true multigenic models of susceptibility to common (i.e., complex) disorders have not been achievable to date.

Lung cancer remains the leading cause of cancer mortality in the Western world, and its incidence is increasing worldwide. Lung cancer is associated strongly with environmental exposures, with the highest population-attributable risk coming from cigarette smoking. Although smoking accounts for the majority of lung cancer cases, the fact that only a minority of smokers develop lung cancer in their lifetimes makes this disease an important model for assessing gene-environment interactions. Because of its clinically poor prognosis, which makes it difficult to conduct efficient family-based linkage analysis of pedigrees for polygenic inheritance, the predominant method used to date in lung cancer has been the candidate gene approach in case-control studies (2–4). The most common method to date of selecting candidates consists of what can be considered as forward selection on the basis of existing knowledge of toxicologic and carcinogenic pathways (e.g., DNA repair, cell cycle, apoptosis) and from functional genomics. Recently, the case-control design has been exploited for Genome-Wide Association Studies (GWAS), and in 2008, several GWAS studies of sporadic lung cancer identified SNPs in the nicotinic receptor genes as important risk factors for lung cancer (5, 6).

The alternate approach offered by You and colleagues (1) is based on the results of the GELCC. The authors undertook the daunting challenge of performing a family-based study of lung cancer in an effort to identify specific causal genes. A recent genome-wide linkage study by the GELCC mapped a major susceptibility locus to 6q23-25. To identify the causal gene in the 6q susceptibility locus, they employed a combination of linkage fine mapping and region-wide SNP association analysis and identified common variants in the RGS17 gene that associate with familial, but not sporadic, lung cancer.

Because RGS17 encodes a recently identified member of the regulator of G-protein signaling (RGS) family and RGS proteins negatively regulate G-protein-related signaling, it hence has functional significance. Moreover, RGS17 is highly expressed in

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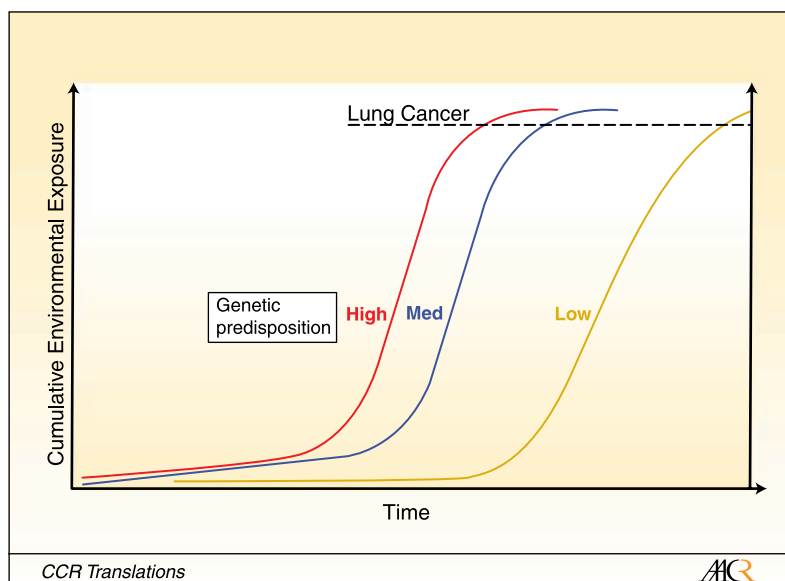


Fig. 1. Gene-environment interactions lead to lung cancer.

tumor tissues, and loss of the RGS17 transcript inhibits the growth of xenografted tumors, making it likely that this gene and its variants may play a role in lung cancer development in familial lung cancer.

Although the study results are interesting, some caveats remain. Firstly, the results are replicated only in familial lung cancer, and not sporadic disease, which accounts for the majority of lung cancer incidence.

Secondly, estimation of separate contributions of genes and environment (in this case, smoking) to lung cancer, including familial tumors, while ignoring their interactions, will incorrectly estimate the proportion of the disease explained by genes, environment, and their joint effects. Hence, the identification of susceptibility in candidate gene studies will provide direct evidence that these genes and their associated pathways are relevant to disease in humans (7). Understanding these pathways will help to determine which agents in a complex mixture, in concert with genetic predisposition, cause disease.

Thirdly, lung cancer is a heterogeneous disease. Larger studies, with detailed information on covariates enabling an

examination of different strata, such as histologic cell type, are needed.

What does this study's finding mean for the practitioner? The identification of RGS17 as the principal candidate gene for familial lung cancer susceptibility on chromosome 6q has potential importance in understanding the mechanisms underlying lung cancer, and thus may be an important locus to investigate for potential chemoprevention efforts in the future. There are not likely to be short-term therapeutic consequences, however, since treatment advances have resulted from discoveries of somatic (tumor), and not germline, genetic analyses (8). Studies such as the one conducted by You and colleagues (1) contribute significantly to our understanding of lung cancer susceptibility and toward the goal of preventive medicine that will allow us to advise patients on disease prevention and outcomes.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### References

1. You M, Wang D, Liu P, et al. Fine mapping of chromosome 6q23-25 region in familial lung cancer families reveals *RGS17* as a likely candidate gene. *Clin Cancer Res* 2009;15:2666-74.
2. Ter-Minassian M, Zhai R, Asomaning K, et al. Apoptosis gene polymorphisms, age, smoking and the risk of non-small cell lung cancer. *Carcinogenesis* 2008; 29:2147-52. doi:10.1093/carcin/bgn205.
3. Zhai R, Liu G, Zhou W, et al. Vascular endothelial growth factor genotypes, haplotypes, gender, and the risk of non-small cell lung cancer. *Clin Cancer Res* 2008;14:612-7. PubMed doi:10.1158/1078-0432.CCR-07-1655.
4. Wu X, Zhao H, Suk R, Christiani DC. Genetic susceptibility to tobacco-related cancer. *Oncogene* 2004;23:6500-23. PubMed doi:10.1038/sj.onc.1207811.
5. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature* 2008;452:537-8. PubMed doi:10.1038/nature06885.
6. Amos CI, Wu X, Broderick P, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nat Genet* 2008;40:616-22. PubMed doi:10.1038/ng.109.
7. Hunter DJ. Gene-environment interactions in human diseases. *Nat Rev Genet* 2005;6:287-98. PubMed doi:10.1038/nrg1578.
8. Heist RS, Christiani D. EGFR-targeted therapies in lung cancer: predictors of response and toxicity. *Pharmacogenomics* 2009;10:59-68. PubMed doi:10.2217/14622416.10.159.