Association of the 15q25 and 5p15 Lung Cancer Susceptibility Regions with Gene Expression in Lung Tumor Tissue

Gord Fehringer1, Geoffrey Liu2,4, Melania Pintilie3, Jenna Sykes3, Dangxiao Cheng2, Ni Liu2, Zhuo Chen2, Lesley Seymour7, Sandy D. Der2, Frances A. Shepherd6, Ming-Sound Tsao2,5, and Rayjean J. Hung1

Abstract

Background: Genome-wide association studies have identified two independent lung cancer susceptibility loci at chromosome 15q25 and one locus at 5p15. We examined the association of genetic variants in these regions with gene expression in lung tumor tissue, in an effort to elucidate carcinogenic mechanisms by which these variants influence lung cancer risk.

Methods: We used data from 2 independent studies of non–small cell lung carcinoma patients: the JBR.10 clinical trial (n = 131) and a University Health Network (UHN) patient sample in Toronto (n = 181). We genotyped seven 15q25 and five 5p15 variants and examined their association with expression profiles of genes in the corresponding regions, measured by Affymetrix HG-U133A.

Results: The minor allele (C) of a variant representing one of the two loci at 15q25 (rs2036534) was associated with increased iron-responsive element binding protein 2 (IREB2) expression in both studies (JBR.10 P = 0.042; UHN P = 0.002). A false discovery rate of 0.05 or less in the UHN sample increased our confidence in this association. The association appears to be more prominent among lung adenocarcinoma patients. We did not detect an association between genotype and expression profile for the other 15q25 locus or for 5p15 variants.

Conclusions: In contrast to previous studies that indicate 15q25 variants are associated with lung cancer risk through an effect on smoking behavior, our results suggest these variants may influence risk through a second mechanism, involving modulation of IREB2 expression.

Impact: This finding expands on potential mechanisms through which 15q25 variants influence lung cancer risk and may have implications for future research on chemoprevention strategies. Cancer Epidemiol Biomarkers Prev; 21(7); 1097–104. ©2012 AACR.

Introduction

Lung cancer, one of the most common cancers worldwide, with approximately 1.6 million cases diagnosed each year, ranks first as a cause of annual global cancer deaths. The 5-year survival rate remains low, at about 15% (1). The primary cause of lung cancer is tobacco smoking (2), but inherited genetic variations also influence lung cancer risk. Genome-wide association studies (GWAS) have identified lung cancer susceptibility regions at chromosomes 15q25 and 5p15 (3–6). Currently, it is not clear how variants in these regions influence risk. Risk-associated variants at 15q25 lie in a region of strong linkage disequilibrium (LD) that comprises several genes including the nicotinic acetylcholine receptor genes (CHRNA5, CHRNA3, LOCH123688, PSMA4, and IREB2). Because the variants at 15q25 are also associated with nicotine dependence (7–10), it has been suggested they influence lung cancer risk at least, in part, through an effect on smoking behavior. Risk-associated variants at 5p15 are also found in a region of high LD and localize to the TERT and CLPTM1L genes. TERT is expressed in 80% of non–small cell lung carcinoma (NSCLC) and may influence carcinogenesis through its role in telomere maintenance. CLPTM1L may play a role in carcinogenesis through an influence on apoptosis (11–14).

In an effort to elucidate the carcinogenic mechanisms by which genetic variants at these regions influence disease risk, we examined the association of genetic variants in lung cancer susceptibility regions with gene expression in tumor tissue of NSCLC patients. Because the main objective was to investigate whether expression of specific genes in these regions mediated the observed associations...
with lung cancer risk, we specifically focused on genetic variants that produced the strongest associations in GWAS and related studies (3, 5, 15, 16). We chose 7 genetic variants at 15q25 to represent the 2 loci known to be associated with disease at this region (2 variants tagged loci 1 and 5 tagged loci 2) and 5 genetic variants to represent 5p15. We used data from 2 independent studies, comparing associations across studies to assess significance after accounting for multiple comparisons.

Materials and Methods

To investigate the association between the genetic variants and gene expression in the corresponding regions, we used data from 2 independent studies: the JBR.10 clinical trial and a patient sample from the University Health Network (UHN) in Toronto. We genotyped seven 15q25 and five 5p15 variants (see Figs. 1 and 2 for variant locations) that were identified by GWAS as associated with lung cancer risk and examined their association with the expression profiles of genes in the corresponding regions measured by Affymetrix HG-U133A. Detailed methods describing recruitment and gene expression microarray profiling for JBR.10 study subjects have been described elsewhere (17, 18). Relevant aspects of methods used for the JBR.10 study, and methods for the UHN study, are described here.

Study subjects

The JBR.10 study was a randomized trial of patients with stage IB or II NSCLC assigned to vinorelbine plus cisplatin (adjuvant treatment arm, n = 242) or to observation (no adjuvant treatment arm, n = 240; ref. 17). Eligible patients were those >18 years of age with completely resected stage IB or II NSCLC, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Subject recruitment began in April of 1994 and the study was closed as of April 2004 (17). Gene expression profiling using lung tumor tissue samples was completed for 133 patients, all with tumor cellularity greater than 20% (18). DNA, which was obtained primarily from normal tissue, was not available for 2 of these samples leaving 131 JBR.10 patients with both gene expression profiles and DNA available for genotyping.

The UHN NSCLC study included patients with stage I or II primary NSCLC retrospectively identified from the UHN tumor bank. These patients had undergone surgery for their cancer at the UHN between 1996 and 2004 but had not received chemotherapy. Only patients with tissue samples of 20% or greater tumor cellularity were included in the study. A total of 190 patients met these criteria and gene expression profiles were obtained for 183 of these (RNA quality was unsuitable for expression profiling for the rest). DNA (obtained mainly from normal tissue) was unavailable for 2 patients, leaving 181 UHN patients with expression profiles and genotype data.

Clinical data, including information on age, sex, smoking status, stage, and histology, was available for both studies.

Laboratory

The Affymetrix HG-U133A GeneChip was used to obtain gene expression profiles for tumor tissue from
JBR.10 patients following RNA extraction from frozen tissue [details are available from a previous publication (18)]. The chip provided expression profiles for all genes in the regions of interest (see Figs. 1 and 2) except LOCI123688 and CLPTM1L, for which probe sets are not available. DNA used for genotyping of JBR.10 subjects was extracted from normal snap-frozen or formalin-fixed and embedded lung tissue using phenol chloroform isoamyl alcohol and genotyped using Sequenom MassArray and TaqMan assay (Table 1 provides a list of genetic variants genotyped, assays used, and genotyping success rate for each variant). For one patient sample, tumor tissue DNA was used for genotyping some variants, as genotyping in normal tissue failed.

For the UHN study, RNA isolation from frozen tissue was carried out with guanidinium thiocyanate-phenol-chloroform reagent. DNA was extracted from normal tissue formalin-fixed, paraffin-embedded samples with chloroform reagent. DNA was extracted from normal snap-frozen or formalin-fixed and embedded lung tissue using phenol chloroform isoamyl alcohol and genotyped using Sequenom MassArray or TaqMan assay (Table 1 provides a list of genetic variants genotyped, assays used, and genotyping success rate for each variant). For one patient sample, tumor tissue DNA was used for genotyping some variants, as genotyping in normal tissue failed.

Data analysis
Microarray data were preprocessed with RMAexpress (version 0.3; ref. 19) for the JBR.10 study and Affymetrix R/Bioconductor (version 2.8.1) for UHN data. For the JBR.10 study, probe sets were annotated with the NetAffx version 4.2 annotation tool and only probe sets with grade A annotation (NA22; ref. 20), corresponding to the genes of interest, were included. Corresponding probe sets were selected for the UHN study. Distance weighted discrimination (21) was used to adjust systematic differences found between JBR.10 batches identified by unsupervised heuristic K-means clustering (Genesis version 1.7.5).

Expression data for both studies were transformed to a Z-score by centering to the mean and scaling to the SD. All genes were profiled with a single probe set except for CHRNA3, which was profiled with 3 probe sets. Pairs of probe sets for CHRNA3 were positively correlated (r ≥ 0.34), and specificity of probe sets for this gene was high (≥0.93). Therefore, the mean of expression results of all 3 probe sets was used to represent expression for this gene in primary analyses, followed by a generalized estimating equation (GEE) approach to verify our results. Multivariate linear regression models were used to analyze the associations between genetic variants and expression of genes in the same region (e.g., 15q25 variants with 15q25 genes) under an additive model using SAS 9.2 (SAS Institute Inc.). This resulted in 40 statistical tests for association. Statistical analyses were first conducted for all patients combined and then stratified by histology (adenocarcinoma and nonadenocarcinoma). Covariates included in models were (i) age (modeled as a continuous variable) and sex and (ii) age, sex, and stage. Because including stage in the model had little influence on regression coefficients and P values, results for models with age and sex are presented here. Genotype was treated as a continuous variable with 0, 1, and 2 representing number of copies of the minor allele. We also conducted stratified analyses by sex and smoking status (current, former, and never) focusing on models in which iron-responsive element binding protein 2 (IREB2) expression was the outcome. The smoking stratification was carried out in UHN only, as the number of never-smokers in JBR10 was not sufficient to conduct a meaningful analysis.

The association of 15q25 haplotypes with IREB2 expression was examined with the haplotype-based association test with GLMs [PLINK version 1.06 (22)]. Genotyped SNPs that best tagged HapMap database SNPs in IREB2 (IREB2 SNPs were not genotyped as we had focused on SNPs that best captured associations with lung cancer in

### Table 1. Variants genotyped, closest gene, assay and genotyping success rate for JBR.10 and UHN patients

<table>
<thead>
<tr>
<th>dbsNP #</th>
<th>polymorphism ID</th>
<th>Type</th>
<th>Gene symbol</th>
<th>Assay</th>
<th>JBR.10</th>
<th>UHN</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs16969668</td>
<td>SNP</td>
<td>CHRNA5</td>
<td>Sequenom</td>
<td>129/131 (98.5)</td>
<td>173/181 (95.6)</td>
<td></td>
</tr>
<tr>
<td>rs6495309</td>
<td>SNP</td>
<td>CHRNA3</td>
<td>Sequenom</td>
<td>129/131 (98.5)</td>
<td>174/181 (96.1)</td>
<td></td>
</tr>
<tr>
<td>rs1051730</td>
<td>SNP</td>
<td>CHRNA3</td>
<td>Sequenom</td>
<td>129/131 (98.5)</td>
<td>174/181 (96.1)</td>
<td></td>
</tr>
<tr>
<td>rs12910984</td>
<td>SNP</td>
<td>CHRNA3</td>
<td>Sequenom</td>
<td>129/131 (98.5)</td>
<td>176/181 (97.2)</td>
<td></td>
</tr>
<tr>
<td>rs578776</td>
<td>SNP</td>
<td>CHRNA3</td>
<td>Sequenom</td>
<td>124/131 (94.7)</td>
<td>179/181 (98.9)</td>
<td></td>
</tr>
<tr>
<td>rs667282</td>
<td>SNP</td>
<td>CHRNA5</td>
<td>Sequenom</td>
<td>129/131 (98.5)</td>
<td>177/181 (97.8)</td>
<td></td>
</tr>
<tr>
<td>rs2036534</td>
<td>SNP</td>
<td>LOCI123688</td>
<td>Sequenom</td>
<td>129/131 (98.5)</td>
<td>172/181 (95.0)</td>
<td></td>
</tr>
<tr>
<td>rs401681</td>
<td>SNP</td>
<td>LOCI123688</td>
<td>Sequenom</td>
<td>129/131 (98.5)</td>
<td>174/181 (96.1)</td>
<td></td>
</tr>
<tr>
<td>rs667282</td>
<td>SNP</td>
<td>CLPTM1L</td>
<td>Sequenom</td>
<td>125/131 (95.4)</td>
<td>166/181 (91.7)</td>
<td></td>
</tr>
<tr>
<td>rs4635969</td>
<td>SNP</td>
<td>CLPTM1L</td>
<td>Sequenom</td>
<td>125/131 (95.4)</td>
<td>174/181 (96.1)</td>
<td></td>
</tr>
<tr>
<td>rs407210</td>
<td>SNP</td>
<td>CLPTM1L</td>
<td>TaqMan</td>
<td>131/131 (100.0)</td>
<td>180/181 (99.4)</td>
<td></td>
</tr>
<tr>
<td>rs2736098</td>
<td>SNP</td>
<td>TERT</td>
<td>Sequenom</td>
<td>128/131 (97.7)</td>
<td>174/181 (96.1)</td>
<td></td>
</tr>
<tr>
<td>rs2736100</td>
<td>SNP</td>
<td>TERT</td>
<td>Sequenom</td>
<td>131/131 (100.0)</td>
<td>175/181 (96.7)</td>
<td></td>
</tr>
</tbody>
</table>
GWAS) were selected to construct haplotypes using the Tagger program (23) incorporated into Haploview version 4.2.

An association was considered to be robust if it reached the conventional level of significance of \( P \leq 0.05 \) in JBR.10, was consistent for direction of effect in both studies, and achieved an false discovery rate (FDR) of \( < 0.05 \) in the larger UHN study [using the Benjamini-Hochberg-Yekutieli procedure (24)]. This assessment was made for primary associations only [main genotype effects for all NSCLC patients combined (i.e., all histologies)].

Results

The basic characteristics of the 2 study populations are summarized in Table 2. Most patients were male (JBR.10: 68%; UHN: 54%) and were current or former smokers (JBR.10: 95%, UHN: 75%). Adenocarcinoma was the predominant histology (JBR.10: 54% UHN: 71%). Mean age was 60.6 in JBR.10 and 68.8 in the UHN study (Table 2).

Linear regression analysis testing the association between genetic variants and tumor tissue gene expression found the minor allele of variant rs2036534 (C allele) to be associated with higher expression of IREB2 in both studies (\( P \leq 0.05 \) in each study; Table 3). The other gene expression-variant associations did not replicate across the 2 studies. The FDR for the association between IREB2 and rs2036534 was less than 0.05 (Benjamini-Hochberg-Yekutieli procedure (24)) in the larger UHN sample, providing confidence that this association is not likely to be a false positive finding resulting from multiple statistical tests. In additional analyses using a GEE approach to account for multiple probe sets (CHRNA3 gene only), we found nearly identical results relative to main analyses in which we averaged the 3 probe sets (e.g., UHN rs16969968: \( \beta = -0.06 \), \( P = 0.45 \)).

Before accounting for multiple comparisons (i.e., based on \( P < 0.05 \)), all of the other 15q25 variants (in addition to rs2036534) were associated with IREB2 expression in the UHN study but not in the JBR.10 study (Table 3). Variants at 15q25 represent 2 distinct LD bins [which account for 2 lung cancer association signals in this region (4)], with one bin tagged by rs16969968 and rs1051730 (denoted as Bin 1) and the other by rs6495309, rs12910984, rs578776, rs667282, and rs2036534 (denoted as Bin 2). The minor alleles for variants in Bin 2 [which are associated with reduced lung cancer risk (15)] were associated with higher IREB2 expression in the UHN study, consistent with the observed direction of effect for rs2036534. Minor alleles for Bin 1 variants [associated with increased lung cancer risk (5)] were associated with lower expression in the UHN study. Because Bin 1 and Bin 2 variants are in weak LD, we conducted further analyses to explore whether the association of Bin 1 variants with IREB2 expression in the UHN study might be explained by Bin 2 variants, as represented by rs2036534. Regression models that included rs2036534 with either of the Bin 1 variants resulted in loss of significance and marked reduction in strength of effect at Bin 1 [e.g., rs16969968: the regression coefficient decreased from \( -0.25 \) (Table 3) to \( -0.12 \), \( P \) value increased from 0.018 (Table 3) to 0.31], while change in the effect of rs2036534 was minimal [the regression coefficient decreased from 0.40 (Table 3) to 0.33; \( P \) value retained significance (\( P = 0.017 \)]. This result indicated that Bin 2 variants best accounted for the association between genetic variation at 15q25 and IREB2 expression in this region.

Results of analyses examining the association of 15q25 variants with IREB2 expression in lung adenocarcinoma patients are shown in Table 4. We found that all 15q25 Bin 2 variants were associated with IREB2 expression in both the JBR.10 and UHN studies in this subgroup. In addition, the association between rs2036534 and IREB2 expression became stronger with a higher regression coefficient and lower \( P \) value. Although Bin 1 variants also showed a statistically significant association with IREB2 expression in the UHN study, significance was again lost after inclusion of the Bin 2 variant rs2036534 into the regression model (data not shown). Among nonadenocarcinoma patients, none of the 15q25 variants showed a significant association with IREB2 expression in either JBR.10 or UHN patients (Supplementary Table S1). However, reduced power due to smaller sample size limited our chances of seeing significant associations in this subgroup.

The relationship between 15q25 Bin 2 variants and IREB2 gene expression was explored further in analyses stratified by sex and smoking status. The trend for an association of the minor allele with higher IREB2 expression was apparent in both sexes, with strength of...
association for Bin 2 variants somewhat stronger in women in both the JBR.10 and UHN studies [e.g., for rs2036534 males: JBR.10 (β = 0.26, P = 0.18, n = 87), UHN (β = 0.34, P = 0.05, n = 92); females: JBR.10 (β = 0.39, P = 0.07, n = 42), UHN (β = 0.46, P = 0.01, n = 80)]. There was no compelling evidence indicating that smoking status modified the association between genotype and gene expression [e.g., for rs2036534 in the UHN data set—current smokers (β = 0.45, P = 0.06, n = 56), former smokers (β = 0.26, P = 0.18, n = 76), never-smokers (β = 0.57, P = 0.12, n = 23)].
None of the genotyped SNPs were in \textit{IREB2}. In fact, rs2036534 was the closest variant lying between \textit{LOC123688} and \textit{PSMA4}, 35,481bp 3' to \textit{IREB2} (Fig. 1). To capture potential unknown variants near \textit{IREB2}, we constructed haplotypes from rs2036534-rs578776 and rs1051730-rs2036534 and tested their association with \textit{IREB2} gene expression. On the basis of HapMap data, \textit{IREB2} rs1051730-rs2036534 and tested their association with constructed haplotypes from rs2036534-rs578776 and (including 5 variants, in the 15q25 lung cancer susceptibility region and \textit{IREB2} associated with the minor allele of rs2036534 produces a favorable response to iron accumulation in the lung, reducing oxidative stress that precipitates inflammation, thus reducing lung cancer risk.

Our findings suggest that there are at least 2 carcinogenic mechanisms that explain how 15q25 variants influence lung cancer risk. So far, the nicotinic acetylcholine receptor genes (\textit{CHRNA3}, \textit{CHRNA5}, and \textit{CHRNB4}) have appeared to be the best candidates to explain the association as previous studies reported Bin 1 and Bin 2 variants to be independently associated with nicotine dependence (7–10). Indeed, it has been argued that smoking behavior accounts for all of the association between genetic variation at this region and lung cancer risk (25). Other investigators, however, report residual association between 15q25 variants and lung cancer risk remains after adjustment for smoking (7, 26), which could be explained by an additional direct effect of variants in this region on lung carcinogenesis (26). Our results suggest that the residual variation not accounted for by smoking may be explained by the influence of genetic variants at 15q25 on \textit{IREB2} expression.

A relationship between \textit{IREB2} expression and NSCLC is biologically plausible. \textit{IREB2} is an RNA binding protein that plays a key role in regulating iron homeostasis (27). High levels of iron in the lungs may produce oxidative stress leading to inflammation and increased lung cancer risk (28). We hypothesize that the increased expression of \textit{IREB2} associated with the minor allele of rs2036534 produces a favorable response to iron accumulation in the lung, reducing oxidative stress that precipitates inflammation, thus reducing lung cancer risk.

Most of the variants chosen for this study have no known functional significance, meaning functional

### Table 4. Association of 15q25 variants with \textit{IREB2} gene expression in JBR.10 and UHN adenocarcinoma patients

<table>
<thead>
<tr>
<th>15q25 Variant (allele designation)</th>
<th>JBR.10</th>
<th>UHN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>$P$</td>
</tr>
<tr>
<td>\textit{IREB2} rs16969968 (G,A)</td>
<td>-0.097</td>
<td>0.656</td>
</tr>
<tr>
<td>rs6495309 (C,T)</td>
<td>0.572</td>
<td>0.033$^b$</td>
</tr>
<tr>
<td>rs1051730 (C,T)</td>
<td>-0.097</td>
<td>0.656</td>
</tr>
<tr>
<td>rs12910984 (A,G)</td>
<td>0.607</td>
<td>0.021$^b$</td>
</tr>
<tr>
<td>rs578776 (C,T)</td>
<td>0.520</td>
<td>0.026$^b$</td>
</tr>
<tr>
<td>rs667282 (T,C)</td>
<td>0.602</td>
<td>0.025$^b$</td>
</tr>
<tr>
<td>rs2036534 (T,C)</td>
<td>0.639</td>
<td>0.009$^b$</td>
</tr>
</tbody>
</table>

$^a$Referent allele, minor allele.

$^b$Statistically significant at $P \leq 0.05$.

$\beta$, regression coefficient.
variants that are in LD with Bin 2 markers are most likely to explain the observed association with IREB2 expression. At the outset of the study, it was not known whether expression of specific genes at the 15q25 or 5p15 regions might explain associations of genetic variants and lung cancer risk. We therefore decided to first attempt to establish associations between markers strongly associated with risk in GWAS and gene expression, which would enable further exploration of the region focusing on functional variants that may explain these associations.

Previous work by Falvella and colleagues found an inverse association between the minor allele of Bin 1 variant rs16969968 and CHRNA5 expression based on 69 normal lung tissue samples from adenocarcinoma patients (29), while Wu and colleagues found an association of the common allele of rs6495309 and higher CHRNA3 expression in 55 normal lung tissue samples from lung cancer patients (16). Similar associations were not found in this study, although it is possible that this is due to the use of expression profiles obtained from normal tissue in the studies discussed above, whereas we obtained expression profiles from tumor tissues. Investigation of the association of 15q25 Bin 2 variants and IREB2 expression in paired normal and tumor tissue can provide insight on whether genetic variation modulates expression in lung tissue before transformation. To date, there has been no previous study examining the association between Bin 2 variants and IREB2 gene expression in lung tissue. Future work could use a fine mapping approach to determine whether variants closer to IREB2 are more strongly associated with IREB2 expression. This approach would be particularly useful in African-Americans who exhibit lower levels of LD, thus permitting better localization of association signals. Fine mapping studies that examine the association of SNPs in this region with risk in African-Americans have already been undertaken (30, 31). In addition, resequencing of this region would further reveal its genetic architecture and may lead to detection of de novo variants at or near IREB2 that are causally related to expression of this gene.

A potential limitation of this study is that undetected confounding due to population stratification may have influenced our results, as ethnicity information was not available for JBR.10 and UHN patients. However, given that the observed allele frequencies are consistent with the HapMap CEU population (data not shown), we do not consider population stratification to be a major concern (32). Another potential limitation is that measurement of gene expression using the Affymetrix HG-U133A GeneChip may be biased due to the presence of G-quadruplex structures which form in the presence of sequential runs of (4) or more) of guanines in probes of some probe sets (33). The IREB2 probe set does not have these sequential runs of guanine so measurement of gene expression will not be directly affected. Still, the presence of these runs of guanine in other probe sets could bias IREB2 gene expression measurement following correction of background noise and normalization. However, this bias is likely to be nondifferential (i.e., bias toward the null) which does not alter our conclusions.

In summary, we have shown an association between IREB2 expression and 15q25 Bin 2 variants (best represented by rs2036534) in patients from 2 independent studies. Our finding suggests that in addition to smoking behavior, there may be a second mechanism that explains the association between the 15q25 susceptibility region and lung cancer risk, operating through modulation of IREB2 gene expression. This finding may have implications on future research of lung cancer chemoprevention strategies such as using iron chelators to compensate for exposure of lung tissue to iron.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors' Contributions
Conception and design: G. Liu, M.-S. Tsao, R. Hung
Development of methodology: G. Liu, D. Cheng, N. Liu, R. Hung
Acquisition of data: D. Cheng, Z. Chen, L. Seymour, S.D. Der, M.-S. Tsao
Analysis and interpretation of data: G. Fehringer, G. Liu, M. Pintilie, J. Sykes, L. Seymour, F.A. Shepherd, R. Hung
Writing, review, and/or revision of the manuscript: G. Fehringer, G. Liu, M. Pintilie, J. Sykes, L. Seymour, F.A. Shepherd, M.-S. Tsao, R. Hung
Administrative, technical, or material support: G. Fehringer, N. Liu
Study supervision: G. Fehringer, G. Liu, R. Hung

Grant Support
This work was supported by Samuel Lunenfeld New Opportunity grants (Dr. Hung) and grants from the Canadian Cancer Society Research Institute (#020214 to Dr. Hung and #020527 to Dr. Tsao), and the Allan Brown Chair in Molecular Genomics (Dr. Liu). Partial funding for the UHN study was provided by Med Biogene Inc. Dr. Tsao is the M. Qasim Choksi Chair in Lung Cancer Translational Research and Dr. Shepherd is the Scott Taylor Chair in Lung Cancer Research. Works carried out at the UHN and Ontario Cancer Institute/Princess Margaret Hospital was supported in part by the Ontario Ministry of Health and Long Term Care. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 30, 2011; revised April 11, 2012; accepted April 17, 2012; published OnlineFirst April 26, 2012.

References


Cancer Epidemiology, Biomarkers & Prevention

Association of the 15q25 and 5p15 Lung Cancer Susceptibility Regions with Gene Expression in Lung Tumor Tissue

Gord Fehringer, Geoffrey Liu, Melania Pintilie, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-11-1123-T

Supplementary Material
Access the most recent supplemental material at:
http://cebp.aacrjournals.org/content/suppl/2012/07/02/1055-9965.EPI-11-1123-T.DC1

Cited articles
This article cites 28 articles, 10 of which you can access for free at:
http://cebp.aacrjournals.org/content/21/7/1097.full.html#ref-list-1

Citing articles
This article has been cited by 4 HighWire-hosted articles. Access the articles at:
/content/21/7/1097.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.