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BRIEF COMMUNICATION

Nicotinic Acetylcholine Receptor Region on Chromosome 15q25 and Lung Cancer Risk Among African Americans: A Case–Control Study

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Genome-wide association studies of white persons with lung cancer have identified a region of extensive linkage disequilibrium on chromosome 15q25.1 that appears to be associated with both risk for lung cancer and smoking dependence. Because studying African American persons, who exhibit lower levels of linkage disequilibrium in this region, may identify additional loci that are associated with lung cancer, we genotyped 34 single-nucleotide polymorphisms (SNPs) in this region (including *LOC123688, PSMA4, CHRNA5, CHRNA3,* and *CHRNB4* genes) in 467 African American patients with lung cancer and 388 frequency-matched African American control subjects. Associations of SNPs in *LOC123688* (rs10519203; odds ratio [OR] = 1.60, 95% confidence interval [CI] = 1.25 to 2.05, *P* = .00016), *CHRNA5* (rs2036527; OR = 1.67, 95% CI = 1.26 to 2.21, *P* = .00031), and *CHRNA3* (rs1051730; OR = 1.81, 95% CI = 1.26 to 2.59, *P* = .00137) genes with lung cancer risk reached Bonferroni-corrected levels of statistical significance (all statistical tests were two-sided). Joint logistic regression analysis showed that rs684513 (OR = 0.47, 95% CI = 0.31 to 0.71, *P* = .0003) in *CHRNA5* and rs8034191 (OR = 1.76, 95% CI = 1.23 to 2.52, *P* = .002) in *LOC123688* were also associated with risk. The functional A variant of rs1696698 in *CHRNA5* had the strongest association with lung cancer (OR = 1.98, 95% CI = 1.25 to 3.11, *P* = .003). These SNPs were primarily associated with increased risk for lung adenocarcinoma histology and were only weakly associated with smoking phenotypes. Thus, among African American persons, multiple loci in the region of chromosome 15q25.1 appear to be strongly associated with lung cancer risk.

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Lung cancer is the leading cause of cancer death in most developed countries, with African American men exhibiting the highest risks of all population groups (1), despite having lower average levels of smoking than white men (2,3). Although the population attributable risk from tobacco smoking for lung cancer is more than 85%, the aggregation of lung cancer among relatives of lung cancer probands indicates that there may be a genetic influence on lung cancer risk (4–7).

Marker densities of approximately one single-nucleotide polymorphism (SNP) per 10 000 base pairs have been used in genome-wide association studies to identify associations of a region of chromosome 15q24–25.1 with lung cancer risk (8–10) and with smoking behavior (11–14). The SNP alleles at rs1051730 were associated with statistically significantly increased risk for lung cancer among white individuals (odds ratio [OR] = 1.31, 95% confidence interval [CI] = 1.27 to 1.36, $P = 1.91 \times 10^{-51}$) (15). Genes in 15q24–25.1 that were associated with lung cancer risk include three subunits of the nicotinic acetylcholine receptor (*CHRNA3*, *CHRNA5*, and *CHRNB4*), *PSMA4*, *LOC123688*, and *IREB2*. African American persons have lower levels of linkage disequilibrium (or association) of marker alleles across 15q24–25.1 than persons of European or Asian ancestry (16). Because studies in African American persons could better identify genes in this region that are associated with lung cancer risk and smoking dependence, we conducted a dense analysis of 34 SNPs (one SNP per 3683 base pairs) across 15q24–25.1 from the centromeric end of *LOC123688* to the telomeric end of *CHRNB4*.

Characteristics of the study population (including 467 self-designated African American case patients with newly diagnosed, histopathologically confirmed lung cancer and 388 frequency-matched self-designated African American control subjects) are shown in Table 1. Case patients were recruited from the University of Texas M. D. Anderson Cancer Center and the Michael E. DeBakey VA Medical Center in Houston, Texas, and the control subjects were recruited from Houston-area community centers and Kelsey–Seybold Clinic, Houston's largest multispecialty physician group practice. These subjects have not been studied previously as part of existing genome-wide association studies but have been studied in candidate gene approaches (18,19). Control subjects had to be free of any previous cancers (excluding nonmelanoma skin cancer) but were not otherwise selected according to health status. The control subjects were frequency matched with the patients by age (±5 years), sex, and ethnicity; however, the matching was incomplete, and so the control population included a higher proportion of women and was younger overall than the case patient population. To date, the response rate for enrolling in the study for both the case patients and the control subjects has been approximately 75%. The Institutional Review Boards at M. D. Anderson Cancer Center, the Michael E. DeBakey VA Medical Center, and the Kelsey–Seybold Clinic approved this research, and each participant signed an informed consent form before completing a personal interview, which obtained information about

CONTEXT AND CAVEATS

Prior knowledge

A region of extensive linkage disequilibrium on chromosome 15q25.1 has been identified in white persons that appears to be associated with risk for lung cancer and smoking dependence. African American persons exhibit lower levels of linkage disequilibrium in this region and so may have additional loci that are associated with lung cancer.

Study design

African American patients with lung cancer and frequency-matched African American control subjects were genotyped for 34 single-nucleotide polymorphisms (SNPs) in 15q25.1, including *LOC123688*, *PSMA4*, and genes for three subunits of the nicotinic receptor (*CHRNA5*, *CHRNA3*, and *CHRNB4*). Associations between each SNP and risk of lung cancer were assessed.

Contribution

Associations were found between three SNPs in *LOC123688*, *CHRNA5*, and *CHRNA3* genes and statistically significantly increased risk of lung cancer. A functional SNP variant in *CHRNA5* had the strongest association. The increased risk was primarily restricted to lung adenocarcinoma histology. These SNPs were only weakly associated with smoking phenotype.

Implications

Multiple loci among African American persons in the 15q25.1 region appear to be associated with lung cancer risk.

Limitations

The study had a limited sample size. There was a low level of linkage disequilibrium among the SNPs and evidence for effects of multiple SNPs across the 15q25.1 region. All case patients and control subjects were from a single institution.

From the Editors

smoking behavior and demographic factors. Smokers were asked to report their use of menthol cigarettes, and former smokers were asked to report the age at which they stopped smoking and the number of years since smoking cessation.

Genotyping was performed with TaqMan Pre-Designed SNP Genotyping Assays (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions with primer sequences provided by the manufacturer. For each SNP, a specific TaqMan Pre-Designed SNP Genotyping Assay Mix (containing probes and primers) was purchased from Applied Biosystems. Polymerase chain reaction (PCR) analysis was performed in a 5-μL solution containing 5 ng of genomic DNA, 2.5 μL of 2× Genotyping Master Mix, 125 μL of 40× Pre-Designed Assay Mix, and 2.375 μL of water in a Dual 384-Well GeneAmp PCR System 9700 (Applied Biosystems). PCR conditions were 10 minutes at 95°C followed by 40 cycles at 95°C for 15 seconds and 60°C for 1 minute. After the PCR, the endpoint fluorescence was read with an ABI Prism 7900HT Sequence Detection System, and the genotype was automatically "called" by use of the SDS software program (version 2.1; Applied Biosystems, Carlsbad, CA). Positive and negative controls were used in each genotyping assay. Comparison of genotyping of white case patients with lung cancer and control subjects that used the TaqMan genotyping platform and that used an Illumina Human HapMap 300 bead array showed a 99.2% concordance between the two methods.

We used SAS/Genetics software, version 9 (SAS Institute, Inc, Cary, NC), to perform univariate, multiple logistic regression and also stepwise forward logistic regression analyses in which we allowed SNPs to enter a model according to the strength of their association. We used the Fisher exact test (20) to assess departure in genotype frequencies from Hardy–Weinberg equilibrium. Markers showing departure at a P value of .01 were flagged but not removed from the analysis (Supplementary Table 1, available online). To assess associations of SNP genotypes with lung cancer risk, we performed simple univariate and multiple logistic regression analyses that were adjusted for age (continuous variable), sex (male or female), and number of pack-years smoked (continuous variable). We also performed a stepwise

Table 1. Demographic characteristics of study participants by case–control status*

Variable	Case patients (n = 467)	Control subjects (n = 388)
Sex, No. (%)		
Male	256 (54.82)	160 (41.24)
Female	211 (45.18)	228 (58.76)
Smoking status,† No. (%)		
Never	52 (11.13)	103 (26.55)
Former	187 (40.04)	140 (36.08)
Current	228 (48.82)	145 (37.37)
Mean age, y (SD)	62.4 (10.1)	55.7 (11.1)
No. of cigarettes per day (SD)	21.2 (12.8)	16.6 (11.8)
Years smoked (SD)	38.0 (12.2)	29.4 (12.6)
No. of pack-years (SD)	41.3 (28.3)	25.5 (22.3)
Histological tumor type, No. (%)		
Ever-smokers		
Adenocarcinoma‡	149 (35.9)	
Squamous carcinoma	127 (30.6)	
BAC, large cell, or NSCC	86 (20.7)	
Small cell	18 (4.3)	
Unknown or missing	35 (8.4)	
Never-smokers		
Adenocarcinoma‡	32 (61.5)	
Squamous carcinoma	4 (7.7)	
BAC, large cell, or NSCC	6 (11.5)	
Small cell	1 (1.9)	
Unknown or missing	9 (17.3)	

* All case–control comparisons were statistically significant ($P < .001$). P values were calculated with a χ^2 test for categorical variables and with a Wilcoxon test for continuous variables. All statistical tests were two-sided. BAC = bronchioalveolar carcinoma; NSCC = non–small cell cancer.

† Never-smokers were defined as those who had smoked fewer than 100 cigarettes in their lifetime; former smokers were defined as those who had quit smoking more than 1 year before diagnosis (case patients) or the interview (control subjects); and current smokers included those who had quit smoking within the past 12 months. Among the smokers, 49% of case patients reported use of mentholated cigarettes compared with 54% of control subjects; this difference was not statistically significantly different.

‡ This category includes four mixed adenocarcinoma and bronchioalveolar carcinomas and one adenosquamous carcinoma. The distribution of histologies in this study was comparable to that in the United States (17).

forward logistic regression analysis in which we added SNPs to the model if they were associated with lung cancer risk (at the $P <$ .20 level) and retained SNPs in the model if they continued to show association (at the $P <$ .15 level), after adjusting for other SNPs in the model. To compare allele frequencies in the histological groups, we performed a case-only logistic regression analysis, treating patients with adenocarcinoma as case patients and patients with squamous carcinoma as the referent group. To evaluate lung cancer risk according to light vs heavy smoking, we stratified the study population by smoking intensity (≤15 or >15 cigarettes per day) and then conducted an unconditional logistic regression analysis of both groups. To assess the reliability by which SNPs and epidemiological variables that predicted lung cancer case status, we evaluated the area under the curve of the receiver operator statistic by evaluating the sensitivity and 1 minus the specificity of classifying case patients and control subjects according to the probability of being a case patient, derived from the logistic regression analysis.

We used the Haploview software program (version 4.1 [http://www.broad.mit.edu/mpg/haploview]; Broad Institute, Cambridge, MA) to summarize and visually display R^2 values. We also performed haplotype-based analyses of multiple genotypes with the PLINK software program (http://pngu.mgh.harvard.edu/purcell/plink/). For this analysis, we used a forward selection approach in which we first incorporated the most statistically significant univariate SNPs. We then added SNPs to the model if there was a statistically significant improvement in the likelihood of the data as assessed by the likelihood ratio test.

Markers were selected for genotyping by the following criteria: known functional effect or previous association with lung cancer risk, observation of the SNP in more than one study, allele frequency of more than 0.05 in African populations, evenness of distribution of SNP spacing across 15q24–25.1, and an R^2 value of less than .70 with other markers (Supplementary Table 2, available online; intermarker R^2 values presented in Figure 1, B). From this procedure, 37 markers were initially selected for analysis, but three markers could not be amplified, leaving a total of 34 for analysis. None of the 34 SNPs were associated with lung cancer risk among never-smokers (52 case patients and 103 control subjects; data not shown), and no association between SNPs and smoking phenotypes were statistically significant after correcting for multiple testing (detailed data available from the authors upon request).

We identified three regions that included statistically significant markers after Bonferroni adjustment (P = .0015; ie, the P value of .05 divided by the 34 SNPs studied). SNPs with the greatest statistical significance within each location (Table 2 and Figure 1, A) were rs10591203 (OR = 1.60, 95% CI = 1.25 to 2.05, P = .00016), which is located in the third intron of *LOC123688*; rs2036527 (OR = 1.67, 95% CI = 1.26 to 2.21, P = .00031), which is located 511 base pairs from the initiation sequence for *CHRNA5*; and rs1051730 (OR = 1.81, 95% CI = 1.26 to 2.59, P = .00137), which is a synonymous SNP in *CHRNA3*. Among African American persons, SNPs that have been associated with lung cancer risk in white persons (rs16969968, rs8031948, rs1051730, rs8034191, and rs10519203) (9) were more strongly associated with lung cancer risk (OR range = 1.61–1.81) (Table 2). The functional A variant of rs1696698 in *CHRNA5* had the strongest association with lung cancer (OR = 1.98, 95% CI = 1.25 to 3.11, P = .003). All statistical tests were two-sided.

In a stepwise logistic regression analysis that adjusted for age, sex, and smoking intensity in pack-years, rs684513 (OR = 0.47, 95% CI = 0.31 to 0.71, P = .0003), which is located in the first intron of *CHRNA5*, and rs8034191 (OR = 1.76, 95% CI = 1.23 to 2.52, P = .002), which is located in *LOC123688*, were also statistically significantly associated with lung cancer risk. SNP rs684513 showed little correlation with either rs8034191 (R^2 = .02) or rs10519203 (R^2 = .04). When we summed the number of adverse alleles (defined as having an OR of >1.0 in a univariate analysis) for rs8034191 and rs684513 (after adjusting for sex, age, and pack-years of smoking) and set zero or one allele as the referent (as identified in 80 control subjects and 73 case patients), risk increased with the number of adverse alleles carried (for two adverse alleles, which was found in 139 control subjects and 202 case patients, OR = 1.6, 95% CI = 1.05 to 2.43; and for three or four adverse alleles, which was found in 48 control subjects and 118 case patients, OR = 3.16, 95% CI = 1.91 to 5.22). Haplotype analysis of the combinations of rs684513 and rs1051730 showed that the haplotypes had a stronger association with lung cancer risk ($P = 8.1 \times 10^{-6}$) than either SNP alone, where the omnibus test jointly tests for an association while adjusting for multiple tests formed by the haplotypes (Supplementary Table 3, available online). Relatively little linkage disequilibrium was evident among African American persons (Figure 1, B), particularly when compared with white persons (8).

We also stratified by the major histological subgroups (Figure 1, C, and Supplementary Table 4, available online). Nearly all statistically significant associations were restricted to adenocarcinomas (at the P = .05 level, in 17 of the 34 tests for adenocarcinoma and one of the 34 tests for squamous carcinoma). The statistically significant association between rs10519203 and lung cancer was stronger among patients with adenocarcinoma (OR = 1.91, 95% CI = 1.38 to 2.65, $P = 9 \times 10^{-5}$) than that among all patients with lung cancer in this study. Only a few SNPs showed statistically significantly different allele frequencies among case patients with adenocarcinoma than among those with squamous carcinoma (Figure 1, C, and Supplementary Table 4, available online), reflecting the limited power for this comparison (eg, for rs8031948 allele frequencies in patients with adenocarcinoma vs those in patients with squamous carcinoma, OR = 1.61, 95% CI = 1.04 to 2.44, P = .023). The receiver operating characteristic curve (a measure of predictive accuracy for case–control status) that included SNPs rs684513 and rs1696698 yielded areas under the receiver operating characteristic curve for these SNPs alone of 0.596 and 0.739, respectively, when age, sex, and pack-years were included. When the analysis was restricted to those with adenocarcinomas, these values were 0.629 and 0.738, respectively, showing slightly higher predictive accuracy from these SNPs alone for adenocarcinoma.

We used measures of nicotine dependence to conduct further analyses of the SNPs that were found to be statistically significantly associated with lung cancer risk in the univariate analyses. First, we examined their association with smoking intensity,

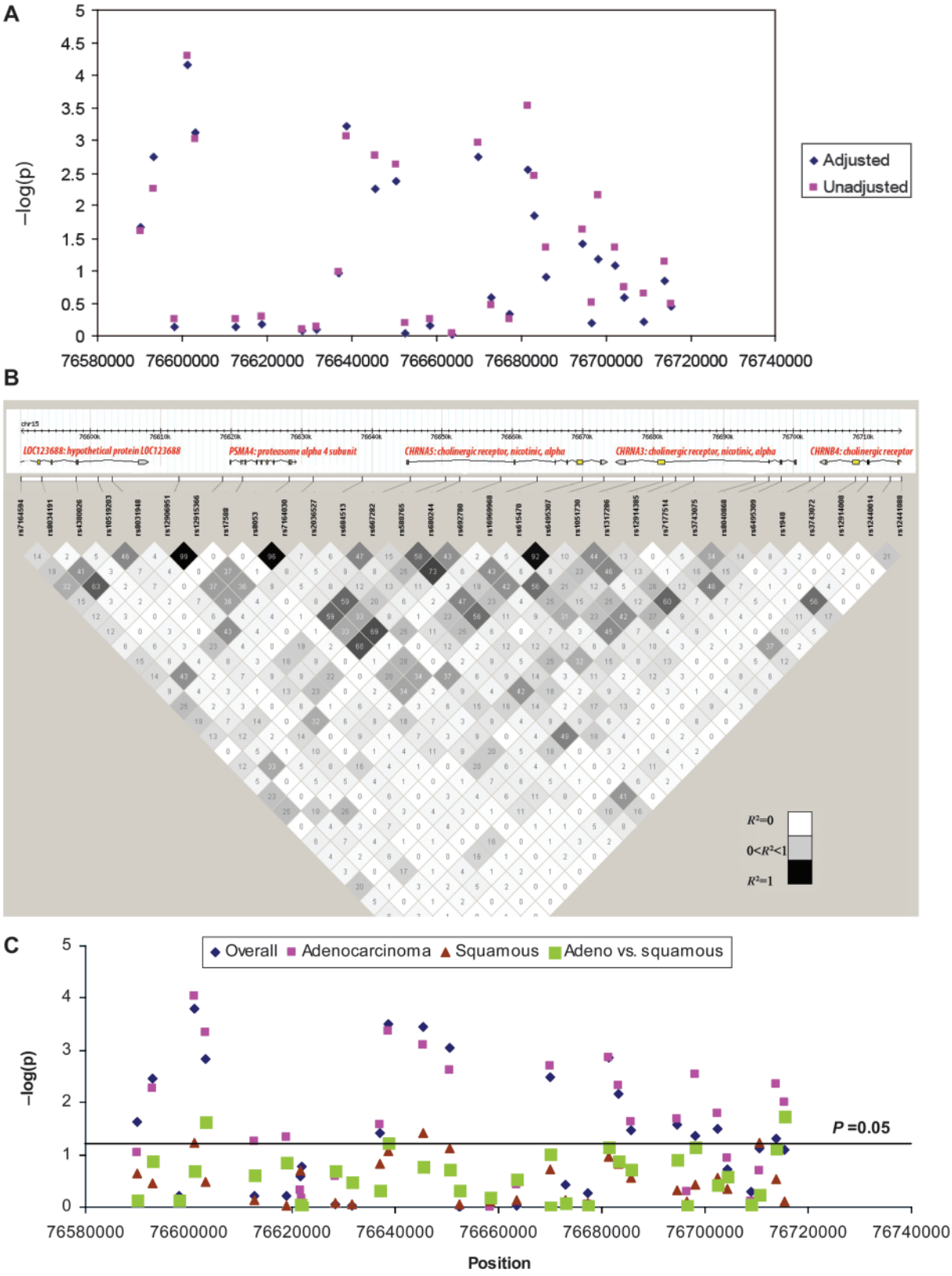

Figure 1. Association of single-nucleotide polymorphisms (SNPs) on chromosome 15q with lung cancer in African Americans. **A**) Association of SNPs with lung cancer before and after adjustment for smoking behavior: The *x*-axis denotes chromosomal position, and the *y*-axis depicts the negative of the base 10 logarithm of hypothesis tests from logistic regression analysis for each SNP either with or without adjustment for sex and smoking behavior (further summary information is provided in Table 2). We displayed the negative logarithm of *P* values so that the more statistically significant tests have higher values on the *y*-axis. **B**) Genes in the analyzed region of chromosome 15q25.1 and

(continued)

Table 2. Unadjusted and adjusted logistic regression analysis of lung cancer risk in ever-smokers by single-nucleotide polymorphisms (SNPs)*

SNP	Chromosomal position†	MAF		OR‡ (95% CI)	*P*	Adj. OR§ (95% CI)	Adj. *P*
		Case patients	Control subjects				
rs7164594	76590112	0.364	0.427	0.77 (0.62 to 0.96)	.01822	0.76 (0.6 to 0.96)	.02387
rs8034191	76593078	0.210	0.157	1.45 (1.08 to 1.94)	.0143	1.61 (1.17 to 2.21)	.00356
rs4380026	76598000	0.106	0.118	0.89 (0.64 to 1.24)	.48577	0.91 (0.64 to 1.3)	.61845
rs10519203‖	76601101¶	0.390	0.291	1.54 (1.23 to 1.94)	.0002	1.60 (1.25 to 2.05)	.00016
rs8031948‖	76603112	0.227	0.160	1.56 (1.18 to 2.08)	.00195	1.65 (1.21 to 2.24)	.00147
rs12906951	76612617	0.154	0.160	0.96 (0.72 to 1.28)	.77453	0.92 (0.68 to 1.26)	.60541
rs12915366	76618808	0.156	0.159	0.96 (0.72 to 1.29)	.80579	0.93 (0.68 to 1.26)	.62532
rs17588	76621588	0.043	0.030	1.47 (0.81 to 2.68)	.20865	1.45 (0.76 to 2.77)	.25467
rs11551779	76621948	0.001	0.005	0.23 (0.02 to 2.19)	.20035	0.20 (0.02 to 2.02)	.17239
rs8053	76628275	0.227	0.216	1.07 (0.82 to 1.39)	.61816	1.02 (0.77 to 1.35)	.89608
rs7164030	76631716	0.227	0.217	1.06 (0.82 to 1.39)	.64431	1.01 (0.76 to 1.34)	.96523
rs7173512	76636969	0.281	0.330	0.84 (0.68 to 1.04)	.10361	0.79 (0.63 to 0.99)	.03943
rs2036527‖	76638670¶	0.284	0.207	1.53 (1.18 to 1.98)	.00124	1.67 (1.26 to 2.21)	.00031
rs684513‖	76645455¶	0.145	0.226	0.58 (0.44 to 0.77)	.00014	0.57 (0.42 to 0.78)	.00036
rs667282‖	76650527	0.230	0.315	0.65 (0.51 to 0.83)	.00053	0.64 (0.49 to 0.83)	.00088
rs588765	76652480	0.299	0.286	1.06 (0.84 to 1.35)	.61934	1.00 (0.78 to 1.30)	.97710
rs680244	76658343	0.422	0.404	1.07 (0.87 to 1.33)	.52037	1.03 (0.82 to 1.30)	.80249
rs692780	76663560	0.233	0.230	1.02 (0.78 to 1.33)	.91214	0.99 (0.74 to 1.32)	.93542
rs16969968	76669980	0.105	0.059	1.89 (1.24 to 2.88)	.00299	1.98 (1.25 to 3.11)	.00331
rs1042500	76670002	0.000	0.004	0.00 (0.00 to ∞)	.97975	0.00 (0.00 to ∞)	.97931
rs615470	76673043	0.405	0.380	1.11 0.89 to 1.38)	.35991	1.11 (0.88 to 1.41)	.36218
rs6495307	76677376	0.416	0.399	1.07 (0.86 to 1.34)	.52175	1.07 (0.85 to 1.35)	.55538
rs1051730‖	76681394	0.167	0.099	1.85 (1.32 to 2.59)	.00036	1.81 (1.26 to 2.59)	.00137
rs1317286	76683184	0.292	0.220	1.47 (1.14 to 1.90)	.00292	1.46 (1.11 to 1.92)	.00693
rs12914385	76685778	0.248	0.193	1.37 (1.06 to 1.79)	.01747	1.36 (1.02 to 1.80)	.03438
rs7177514	76694461	0.261	0.323	0.76 (0.60 to 0.95)	.01581	0.76 (0.59 to 0.97)	.02627
rs3743075	76696507	0.439	0.456	0.93 (0.75 to 1.16)	.52849	0.98 (0.78 to 1.24)	.86989
rs80408687	76698236	0.390	0.322	1.38 (1.09 to 1.75)	.00697	1.30 (1.01 to 1.67)	.04383
rs6495309	76702300	0.206	0.255	0.76 (0.59 to 0.98)	.03227	0.74 (0.56 to 0.98)	.03274
rs1948	76704454	0.199	0.231	0.81 (0.62 to 1.06)	.13346	0.82 (0.62 to 1.10)	.18575
rs3743072	76708817	0.089	0.115	0.77 (0.55 to 1.08)	.13370	0.88 (0.61 to 1.27)	.49991
rs12914008	76710560	0.009	0.0145	0.59 (0.21 to 1.65)	.31774	0.37 (0.12 to 1.10)	.07398
rs12440014	76713781	0.184	0.230	0.76 (0.59 to 0.99)	.04338	0.75 (0.57 to 1.00)	.04792
rs12441088	76715319	0.275	0.318	0.81 (0.63 to 1.03)	.07955	0.79 (0.61 to 1.03)	.07874

* Additive model assumes that the log risk increments by the number of minor alleles. Adj. = adjusted; CI = confidence interval; MAF = minor allele frequency; OR = odds ratio.

† Position along the chromosome from telomere.

‡ Unadjusted for any covariates.

§ Adjusted for age, sex, and pack-years.

‖ *P* value is less than .00147 (the Bonferroni-adjusted level defined by testing 34 markers).

¶ Pairwise R^2 values among statistically significant markers were as follows rs10519203 vs rs8031948, R^2 = .46; rs2036527 vs rs684513, R^2 = .06; and rs684513 vs rs667282, R^2 = .47.

adjusting for age, sex, and case–control status. Among African American individuals, rs1051730 was associated with number of cigarettes smoked per day in the case patients (individuals with no risk genotypes smoked 20.7 cigarettes per day, individuals with one risk allele smoked 22.5 cigarettes per day, and individuals with two risk genotypes smoked 26.1 cigarettes per day, P = .02), but no statistically significant trend was noted among control subjects. rs16969968, which is strongly predictive of nicotine dependence in white individuals, was not associated with smoking behavior in either African American case patients or African American control

Figure 1 (continued).

patterns of linkage disequilibrium. **Shaded squares** = correlation among the SNPs that were analyzed across the region, with **gradation in shading** representing the strength of the correlation; **light shading** = R^2 = 0; **dark black** = R^2 > .95. **C**) Allelic tests of associations between SNPs and lung cancer risk according to histological subgroups. Allele frequencies of adenocarcinoma, squamous, and all histological types of lung cancer in case patients were compared with allele frequencies in control participants by use of logistic regression. In addition, the allele frequencies in case patients with adenocarcinoma lung cancer (the referent) were compared with allele frequencies in those with squamous lung cancer by use of logistic regression with a case-only design. The **horizontal line** = position of a *P* value of .05.

participants. The prevalence of the risk allele rs1051730 increased progressively as the smoking intensity increased. Among those who smoked 1–10, 11–20, or 21 or more cigarettes per day, the prevalences of the risk allele were 0.114, 0.171, and 0.214, respectively ($P = .006$), in case patients and 0.079, 0.102, and 0.144, respectively, in the control subjects ($P = .097$). We also stratified the data by the median smoking intensity in the control subjects (ie, <15 vs ≥15 cigarettes per day) (Supplementary Table 5, available online). With the exception of risks associated with SNP rs8031948, all estimates of lung cancer risk were slightly higher in the subgroups with lower smoking exposure than in those with heavier exposure. However, when the analysis was dichotomized at the control median of 20 pack-years, this pattern was not evident (Supplementary Table 6, available online).

Although this report provides new details about associations of SNPs in the chromosome 15q region with lung cancer risk, the study has some limitations. The study has a limited sample size, which impeded our ability to contrast the strength of evidence associating specific alleles with lung cancer risk. The low level of linkage disequilibrium among the SNPs and evidence for effects of multiple SNPs across the region suggests that there are effects from multiple loci, but it is still possible that unmeasured variants could be associated with these multiple loci. Finally, although all of the case patients and control subjects were derived from a single center, it is possible that some degree of population structure influences our findings. Further studies of larger numbers of African American individuals with allowance for variations in their ethnic background would permit a more precise delineation of the number of loci and the specific alleles in this region that influence lung cancer risk.

Results of this detailed genetic study of the 15q24–15q25.1 region among African American case patients with lung cancer and African American control subjects support an association between genes in this region and lung cancer in this high-risk ethnic group. In addition, if an SNP was associated with increased risk of lung cancer among white persons, the association observed was even stronger among African American persons. A joint modeling analysis across the region indicated that at least two loci, as represented by SNPs rs684513 and rs803419, contributed to this association. Unlike results among white and Chinese persons that showed little variation by histological subtype (15,21), the association among African American persons was strongest for adenocarcinoma. This finding could indicate the existence of a risk-susceptibility allele conferring an increased risk for adenocarcinoma that is present in African American persons but absent in white persons, or this finding could be due to chance. Among never-smokers, neither SNP rs684513 nor SNP rs803419 was associated with lung cancer risk. However, the association was stronger among lighter smokers than among heavier smokers, which supports the concept that there is a direct association of SNPs in this region with lung cancer, beyond a weaker association with smoking behavior. Thus, there appears to be an independent association between SNPs in this region of chromosome 15q and lung cancer risk that may include contributions from multiple genetic factors.

Supplementary Data

Supplementary data can be found at http://www.jnci.oxfordjournals.org/.

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Notes

G. B. Mills is a scientific advisor for Arexis Biotechnologies and has stock options from them;

is a consultant for Amira Pharmaceuticals, Inc; is a member of the scientific advisory committee of the Canada Foundation for Innovation; is a scientific advisor for Catena Pharmaceuticals and has stock options from them; is a consultant for Enzon, Genetech, and Genome British Columbia; is a speaker or holds a preceptorship and is a cousultant for GlaxoSmithKline; has stock options from Lpath Therapeutics, Inc; is a scientific advisor for N of One Oncology Council; is a scientific advisor for PTV Sciences, LP; is a consultant for and owns stock in Semafore Pharmaceuticals; is a consultant for Signal Pharmaceuticals, LLC; and is a consultant for and has a scientific speaker agreement with Wyeth Pharmaceuticals. The authors had full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

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