

Smokers with the *CHRNA* Lung Cancer–Associated Variants Are Exposed to Higher Levels of Nicotine Equivalents and a Carcinogenic Tobacco-Specific Nitrosamine

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Abstract

A locus at 15q24/15q25.1, which includes the nicotinic acetylcholine receptor A subunits 3 and 5 (*CHRNA3* and *CHRNA5*) genes, has recently been associated with lung cancer risk, self-reported number of cigarettes smoked per day, and a nicotine dependence scale. It is not clear whether the association with lung cancer is direct or mediated through differences in smoking behavior. We used urinary biomarkers to test whether two linked lung cancer risk variants in *CHRNA3* (rs1051730) and *CHRNA5* (rs16969968) are associated with intensity of smoking and exposure to a tobacco-specific carcinogenic nitrosamine per cigarette dose. We studied 819 smokers and found that carriers of these variants extract a greater amount of nicotine ($P = 0.003$) and are exposed to a higher internal dose of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone ($P = 0.03$) per cigarette than noncarriers. Thus, smokers who carry the *CHRNA3* and *CHRNA5* variants are expected to be at increased risk for lung cancer compared with smokers who do not carry these alleles even if they smoked the same number of cigarettes. Number of cigarettes per day, even if it could be accurately assessed, is not an adequate measure of smoking dose. [Cancer Res 2008;68(22):9137–40]

Introduction

Three whole-genome association studies (GWAS) recently identified a region of strong linkage disequilibrium on the long arm of chromosome 15 as being a susceptibility locus for lung cancer. The most likely candidate genes in this region are those that encode subunits of nicotinic acetylcholine receptor A (*CHRNA3* and *CHRNA5*). The conclusions from the three studies differed on whether the link to lung cancer is direct or mediated through differences in smoking behavior. Previous reports had strongly associated these two genes with self-assessed nicotine dependence (1, 2). The GWAS by Thorgeirsson and colleagues (3) confirmed these results by agnostically associating single nucleotide polymorphisms (SNP) at 15q24/15q25.1 with self-reported number of cigarettes smoked per day and a nicotine dependence scale. The other two GWAS by Amos and colleagues (4) and Hung and colleagues (5) also considered the lifetime smoking history of their cases and controls but found little evidence that this locus

influences smoking behavior. Thus, these authors concluded that the association was primarily with lung cancer. Because the association of smoking with this disease is very strong, it is difficult to detect any residual independent association with a gene variant that primarily acts through increasing exposure to smoking. Here, we show with biomarkers that carriers of the risk variants in *CHRNA3* and *CHRNA5* smoke more intensively and are exposed to a higher internal dose of a carcinogenic tobacco-specific nitrosamine per cigarette dose than noncarriers. These data are consistent with the overall increased lung cancer risk associated with this locus and suggest that number of cigarettes per day, even if it could be accurately assessed, is not an adequate surrogate for smoking dose when examining the independent effect of the 15q locus on lung cancer.

Materials and Methods

We first studied 583 men and women of European, Japanese, or Native Hawaiian ancestry who were long-term smokers of >10 cigarettes day. Participants were randomly selected among members of the Multiethnic Cohort Study (88%) or controls of several completed population-based case-control studies (12%) living on Oahu, Hawaii (6–8). Other inclusion criteria included having no previous history of invasive cancer, having both parents of Japanese or European ethnicity, or of any amount of Native Hawaiian ancestry, and smoking at least 10 cigarettes per day. These individuals were recontacted for this study and instructed on how to record their food consumption for 3 d, as well as to collect a 12-h, overnight urine sample at the end of those 3 d. A blood sample was then collected and a short questionnaire (including tobacco use during the previous 3 d) was administered. The overall target sample size for this study was 100 in each sex and ethnic group. A total of 596 participants completed all aspects of the study, corresponding to a participation rate of 64.4%. Eight subjects were excluded for reporting to smoke fewer than the required 10 cigarettes per day during data collection, and five were excluded for missing covariate.

Subjects were genotyped for the synonymous variant rs1051730 in exon 5 of *CHRNA3* and the nonsynonymous variant rs16969968 in *CHRNA5*, the candidate SNPs that most likely to be causal in the 15q region associated with lung cancer in the three published GWAS (3–5). DNA was extracted from lymphocytes and the two variants were genotyped with the Taqman allele discrimination assay (Applied Biosystems). The genotype frequencies were consistent with Hardy-Weinberg equilibrium in each ethnic group ($P > 0.05$). Concordance rate across the ~10% blinded duplicate samples genotyped with the study samples was 100%. The genotyping call rate was 99%. The frequency of the T allele for rs1051730 was 0.34 in European Americans, 0.19 in Native Hawaiians, and 0.03 in Japanese Americans. The corresponding frequencies of the A allele for rs16969968 were 0.34, 0.20, and 0.03.

To assess total nicotine, and hence tobacco smoke exposure, the urinary concentration of the sum of nicotine and five nicotine metabolites was determined. The sum of these six compounds, which account for 75% to 95% of the nicotine dose, is referred to as nicotine equivalents and is

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considered the most comprehensive measure of exposure to nicotine (9). Specifically, we measured the molar concentrations of total nicotine (free plus nicotine *N*-glucuronide), total cotinine (free plus cotinine *N*-glucuronide), total *trans*-3'-hydroxycotinine (3-HC; free plus 3-HC *N*- and *O*-glucuronide), as well as a metabolite of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its detoxification product NNAL-glucuronide (NNAL-Gluc), in the 12-h urine. Nicotine metabolites were measured by gas chromatography-mass spectrometry, and nicotine equivalents were calculated as the sum of the molarity of total nicotine, total cotinine, and total 3-HC. NNK metabolites were measured by gas chromatography with nitrosamine selective detection (10, 11). Based on 65 blind duplicate pairs analyzed with the study samples for total nicotine and total cotinine, and six pairs for total 3-HC, the intraclass correlation coefficient was 0.98, 0.96, and 0.62, respectively. NNK metabolites were determined as described with slight modifications (12).

We sought to replicate findings from the Hawaii study in two studies conducted at the University of Minnesota (UMN) that collected first morning urine. UMN Study 1 (UMN-1) included 99 participants (only 2 of which were non-White) in a clinical trial (the Tobacco Reduction Intervention Program Study), which recruited smokers of more than 14 cigarette per day and aged 18 to 70 y who were interested in reducing cigarette use in the next 30 d (13). UMN Study 2 (UMN-2) included 137 smokers (118 European Americans, 15 African-Americans, and 4 Asian/Pacific Islanders). Smokers of 10 to 40 "light" cigarettes (0.7–1.0 mg nicotine/cigarette) per day, aged 18 to 70 y, who were interested in quitting smoking were recruited via advertisement. To be eligible for both UMN studies, smokers had to (a) be in good physical health, (b) have no contraindication to nicotine replacement therapy, (c) be in good psychiatric health, (d) not be using other tobacco products, and (e) not be pregnant or nursing. In both studies, the average number of cigarettes per day was computed from a daily diary and a first morning urine sample was collected from each subject. In these studies, the frequency of the rs16969968 A allele was 0.35 in European Americans and 0.10 in African-Americans. The genotype frequencies were consistent with Hardy-Weinberg equilibrium (African-Americans, $P > 0.05$; Caucasians, $P = 0.01$). Concordance rates across the ~15% blinded duplicate samples genotyped were 97% to 100% and the genotyping call rate was 100%.

A square-root transformation was used for nicotine equivalents to achieve normal distribution. The sum of NNK metabolites was log transformed. Least-square means for these two variables were computed for each genotype using the general linear model procedure in Statistical Analysis System 9.0 (SAS, Inc.) adjusting for age, sex, race/ethnicity, cigarettes per day, and body mass index (BMI) and further for nicotine equivalents. In the pooled analysis, an adjustment variable for study was included. Tests of interaction were conducted between genotype and study to identify modifying effects but were not statistically significant and, therefore, were not included in the final models. Tests for significance were two tailed with an α level of 0.05.

Results

Main characteristics of study participants are shown in Table 1. In the Hawaii study, we found that subjects with the *CHRNA3* T allele or the *CHRNA5* A allele had a higher age-, sex-, and race-adjusted mean nicotine equivalents with a dominant genetic effect (Table 2). Adjustment for other determinants of nicotine equivalents, particularly number of cigarettes per day, attenuated this association only slightly, indicating that carriers of the T or A allele are exposed to higher levels of nicotine per cigarette dose. The mean sum of the urinary NNK metabolites (NNAL + NNAL-Gluc) also increased with the number of T and A alleles, even after adjusting for potential confounders. These associations were significant in each sex and in European Americans for the A allele. The T and A alleles were less common in Japanese Americans (3%) and Native Hawaiians (~19%) than European Americans (34%), and thus, the power was lower in these groups.

The results from the UMN studies are shown in Table 3. Similar increasing trends in the mean nicotine equivalents and total NNAL were observed with the number of *CHRNA5* A alleles in these replication data sets, although the differences in the means did not reach statistical significance. Because there was no heterogeneity across studies, we combined the three data sets to compute mean nicotine equivalents and total NNAL by *CHRNA5* genotype

Table 1. Main characteristics of participants by study

| | Study | | |
|-----------------------------------|------------------|-------------------|-------------------|
| | Hawaii study | UMN-1 | UMN-2 |
| <i>n</i> (%) | 583 | 99 | 137 |
| Males (%) | 50.4 | 49.5 | 55.5 |
| Race/ethnicity (%) | | | |
| European American | 33.9 | 97.0 | 86.1 |
| Native Hawaiian | 32.8 | 0 | 0 |
| Japanese American | 33.3 | 0 | 0 |
| Other* | 0 | 3.0 | 13.9 |
| Age (y) | 61 (57–66) | 46 (23–52) | 43 (23–32) |
| BMI (kg/m ²) | 26.1 (23.2–30.0) | 27.7 (23.1–31.3) | 27.4 (23.5–32.1) |
| Cigarettes per day | 20.0 (16.7–28.0) | 25.0 (20.0–30.0) | 20.0 (15.0–25.0) |
| Smoking duration (y) | 43.0 (38.0–48.0) | 28.0 (22.0–35.0) | 24.0 (11.0–34.0) |
| Nicotine equivalents [†] | 57.9 (40.9–85.7) | 87.2 (51.7–127.8) | 60.0 (43.1–100.4) |
| Total NNAL [‡] | 1.28 (0.83–1.87) | 2.05 (1.39–3.05) | 0.91 (0.58–1.29) |

NOTE: Values are medians and interquartile ranges, unless otherwise indicated.

* African-American or Asian/Pacific Islander in the UMN studies.

† Sum of nicotine, cotinine, 3-HC, and their respective glucuronides (in nmol/mg creatinine).

‡ Sum of free NNAL and NNAL-Gluc (in pmol/mg creatinine). Four and one subjects had missing total NNAL in the Hawaii study and UMN-2 study, respectively.

Table 2. Geometric means (95% confidence intervals) for nicotine equivalents and NNK internal dose by *CHRNA3* and *CHRNA5* genotype in the Hawaii study

| Gene | Genotype | Nicotine equivalents | | | | | | | | | Total NNAL* | | | | |
|-------------------------------|----------|----------------------|--|----------------|-----------------|---------------------------------|------------------|----------------|------|---------------|----------------|------------------|----------------|-----------------|----------------|
| | | n | Age-, sex-, and race-adjusted model [†] | | | CPD-adjusted model [‡] | | | n | Mean (95% CI) | P [§] | P | P [¶] | | |
| | | | Mean (95% CI) | P [§] | P | P [¶] | Mean (95% CI) | P [§] | | | | | | P | P [¶] |
| <i>CHRNA3</i> (rs1051730) | GG | 393 | 59.0 (55.4–62.6) | 0.004 | 0.01 | 0.20 | 59.1 (55.7–62.6) | 0.004 | 0.01 | 0.31 | 390 | 1.20 (1.13–1.27) | 0.14 | 0.33 | 0.58 |
| | GT | 157 | 68.7 (62.6–75.1) | | | | 70.2 (57.5–84.3) | | | | 156 | 1.31 (1.19–1.45) | | | |
| | TT | 31 | 72.3 (59.0–87.0) | | | | 70.2 (57.5–84.3) | | | | 31 | 1.32 (1.06–1.65) | | | |
| <i>CHRNA5</i> (rs16969968) | GG | 393 | 64.2 (57.7–71.1) | 0.003 | 0.01 | 0.09 | 59.2 (55.8–62.6) | 0.003 | 0.01 | 0.15 | 390 | 1.19 (1.12–1.27) | 0.04 | 0.11 | 0.26 |
| | AG | 159 | 61.0 (53.9–68.6) | | | | 68.6 (62.8–74.7) | | | | 158 | 1.33 (1.21–1.47) | | | |
| | AA | 31 | 78.0 (71.7–84.5) | | | | 73.3 (60.2–87.5) | | | | 31 | 1.42 (1.14–1.77) | | | |

Abbreviations: CPD, cigarettes per day; 95% CI, 95% confidence interval.

*Sum of urinary NNAL and NNAL-Gluc (in pmol/mg creatinine), adjusted for age, sex, race/ethnicity, and cigarettes per day.

† Sum of urinary nicotine, cotinine, 3-HC, and their respective glucuronides (in nmol/mg creatinine), adjusted for age, sex, and race/ethnicity.

‡ Further adjusted for cigarettes per day and BMI.

§ P for dominant model of inheritance.

|| P for additive model of inheritance.

¶ P for recessive model of inheritance.

adjusting for cigarettes per day using all subjects. Differences in mean nicotine equivalents and total NNAL were observed, with P values that were as strong as those for the Hawaii study (Table 3).

Discussion

Nicotinic acetylcholine receptor subunit genes code for proteins that form receptors present in neuronal and other

tissues, such as alveolar epithelial cells and pulmonary neuroendocrine cells, and bind to nicotine (14). Sequence variants in this cluster of genes on chromosome 15 have been associated with increased (self-reported) cigarette dose and nicotine dependence (2).

Our study, which uses nicotine equivalents as a more accurate reflection of tobacco smoke exposure than self-reported cigarettes per day, further indicates that carriers of these variants smoke

Table 3. Geometric means (95% confidence intervals) for nicotine equivalents and total NNK exposure by *CHRNA5* genotype in two UMN studies and in all studies combined

| Study | rs16969968 genotype | Nicotine equivalents | | | | | | | | | Total NNAL* | | | | |
|-------|---------------------|----------------------|---------------------------------|----------------|-----------------|---------------------------------|--------------------|----------------|------|---------------|----------------|------------------|----------------|-----------------|----------------|
| | | n | Age-adjusted model [†] | | | Multivariate model [‡] | | | n | Mean (95% CI) | P [§] | P | P [¶] | | |
| | | | Mean (95% CI) | P [§] | P | P [¶] | Mean (95% CI) | P [§] | | | | | | P | P [¶] |
| UMN-1 | GG | 41 | 90.3 (58.4–129.2) | 0.72 | 0.41 | 0.26 | 93.5 (61.0–132.8) | 0.47 | 0.31 | 0.28 | 41 | 3.00 (2.38–3.77) | 0.31 | 0.21 | 0.09 |
| | AG | 48 | 81.5 (48.9–122.2) | | | | 79.4 (47.4–119.7) | | | | 48 | 3.14 (2.44–4.04) | | | |
| | AA | 10 | 108.5 (59.8–171.6) | | | | 107.6 (59.4–170.0) | | | | 10 | 3.81 (2.73–5.31) | | | |
| UMN-2 | GG | 74 | 49.7 (37.0–64.2) | 0.30 | 0.38 | 0.20 | 53.1 (40.8–67.2) | 0.36 | 0.42 | 0.21 | 73 | 1.89 (1.66–2.15) | 0.83 | 0.96 | 0.94 |
| | AG | 43 | 53.5 (36.9–73.2) | | | | 56.1 (40.0–74.9) | | | | 43 | 1.86 (1.59–2.17) | | | |
| | AA | 20 | 63.1 (41.6–89.1) | | | | 65.4 (44.7–90.0) | | | | 20 | 1.89 (1.57–2.27) | | | |
| All** | GG | 508 | 60.5 (54.2–68.1) | 0.003 | 0.005 | 0.02 | 61.2 (54.2–68.7) | 0.01 | 0.02 | 0.04 | 504 | 1.48 (1.32–1.65) | 0.03 | 0.09 | 0.21 |
| | AG | 250 | 67.0 (58.1–76.6) | | | | 66.7 (58.1–76.0) | | | | 249 | 1.59 (1.40–1.80) | | | |
| | AA | 61 | 77.7 (64.2–92.4) | | | | 76.1 (63.2–90.3) | | | | 61 | 1.70 (1.42–2.04) | | | |

*Sum of urinary NNAL and NNAL-Gluc (in pmol/mg creatinine), adjusted for age, sex, race/ethnicity, and cigarettes per day.

† Sum of urinary nicotine, cotinine, 3-HC, and their respective glucuronides (in nmol/mg creatinine), adjusted for age, sex, and race/ethnicity.

‡ Further adjusted for cigarettes per day and BMI.

§ P for dominant model of inheritance.

|| P for additive model of inheritance.

¶ P for recessive model of inheritance.

** Models are further adjusted for study.

more intensively, resulting in higher exposures to nicotine, to NNK, and most likely to other tobacco smoke carcinogens.

NNK is a tobacco-specific nitrosamine that is an effective pulmonary carcinogen in every animal species tested (15). A total dose of only 6 mg/kg NNK, administered by s.c. injection over a period of 20 weeks, induced a significant incidence of lung tumors in rats (16). NNK given in the drinking water to rats at a concentration of 1 ppm for 105 weeks caused a significant incidence of lung tumors, and similar treatment of rats with 5 ppm of NNK or its metabolite NNAL induced lung tumors in >85% of the rats (17). A smoker is exposed to an estimated 0.5 mg/kg body weight NNK in 30 years of smoking (18). The major mechanism by which NNK causes lung cancer is through DNA adduct formation, resulting in mutations in critical growth control genes, such as *K-ras* (15). The strong parallels that exist in mechanisms of NNK carcinogenesis between rodents and humans led the IARC to classify NNK as “carcinogenic to humans” (18). Thus, our data indicate that smokers who carry the *CHRNA3* or *CHRNA5* variant are expected to be at increased risk of lung cancer compared with smokers who do not carry these alleles—even if they smoke the same number of cigarettes—because they smoke more intensively and are, therefore, exposed to greater levels of carcinogens.

We also note that the population frequencies of these variants suggest that they are unlikely to explain, by themselves, the ethnic/racial differences in lung cancer risk among smokers that we have

documented in these populations because risk is higher among Native Hawaiians and lower in Japanese Americans compared with European Americans (19, 20).

Our study does not address the possibility that the *CHRNA3/CHRNA4* SNPs exert an independent effect on lung cancer risk, as it has been suggested based on the role these receptors may play in mediating the angiogenic and tumor growth effects of NNK (5). However, these effects may not be critical because similar receptor-mediated effects would be expected from nicotine (which is not a carcinogen), the concentration of which is considerably greater ($\times 10,000$) than NNK. Nevertheless, our data clearly indicate that a simple adjustment for number of cigarettes per day is inadequate to control for smoking dose in studies examining the independent association of these variants with smoking-associated lung cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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