

Associations between phenylthiocarbamide gene polymorphisms and cigarette smoking

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[Received 25 April 2005; accepted 14 July 2005]

Phenotypic evidence indicates that the ability to taste the bitter compounds phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP) may protect against cigarette smoking. In this study, PTC gene haplotypes were found to be associated with both the odds of being a smoker and the importance of cigarette taste as a smoking motive. Smokers ($n=384$) and nonsmokers ($n=183$) were genotyped for polymorphisms that affect taste sensitivity to PTC and PROP. The “taster” PAV haplotype, relative to the “nontaster” AVI haplotype, was predicted to be associated with reduced odds of being a smoker and lower taste motivation as measured by the Wisconsin Inventory of Smoking Dependence Motives–68 taste/sensory processes scale. The results did not support the predicted association between the PAV and AVI haplotypes and smoker odds, but the AAV haplotype, which confers intermediate PTC/PROP taste sensitivity, was associated with reduced smoker prevalence (49% vs. 70%), $\chi^2(1, N=567)=10.392, p=.001$. The predicted relationship between PAV and AVI and taste motivation was found, $F(2, 348)=3.303, p=.038$. The results encourage further exploration of the role of taste/sensory processes in tobacco dependence.

Introduction

The ability to taste the bitter compounds phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP) is one of the best-studied inherited traits in humans (Fox, 1932; Guo & Reed, 2001; Reddy & Rao, 1989; “Tastebblindness,” 1931). PTC and PROP are synthetic compounds with a N–C=S moiety. Taste sensitivity to these compounds has a bimodal distribution, which gives rise to the practice of dichotomizing populations into “tasters” and “nontasters.” Bitter taste perception is the most complex

of the basic tastes and involves multiple taste transduction systems and receptors (Drewnowski, 2001). Thus the specific mechanisms involved in the perception of PTC/PROP as well as the genes underlying PTC/PROP taste sensitivity may differ from those involved in the perception of other bitter tastes, although some generalization can be made from PTC/PROP taste perception to the perception of other bitter compounds such as caffeine (Drewnowski, 2001).

Phenotypic evidence indicates that the ability to taste PTC/PROP may protect against cigarette smoking. Kaplan and Glanville (1964) reported lower PROP taste sensitivity and fewer PROP tasters among smokers than nonsmokers. More recently, Enoch, Harris, and Goldman (2001) reported that the ability to taste PTC was less prevalent among smokers than either nonsmokers or people who smoked less than 8 cigarettes/day. A similar relationship between PTC/PROP taste perception and decreased alcohol consumption has been reported (see Bachmanov et al., 2003, for review).

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Kim et al. (2003) showed that mutations in a bitter taste receptor gene located on chromosome 7q explain 55%–85% of the observed variance in the ability to taste PTC. This gene has been assigned the name PTC by the Human Gene Nomenclature Committee, but it also is referred to as T2R38 or TAS2R38. Kim et al. (2003) identified three single nucleotide polymorphisms (SNPs) in the PTC gene. These SNPs are at base pair 145 (G to C, resulting in alanine to proline at amino acid 49), base pair 785 (T to C, resulting in valine to alanine at amino acid 262), and base pair 886 (A to G, resulting in isoleucine to valine at amino acid 296). Combinations of polymorphisms at these three PTC SNPs create haplotypes named for the amino acid changes (A49P, V262A, and I296V). For example, if position 145 is C, position 785 is C, and position 886 is G, then the amino acids at these positions are proline, alanine, and valine, and the haplotype name is PAV. The two most common haplotypes by far are PAV and AVI, but three less common haplotypes (AAI, AAV, and PVI) have been reported (Kim et al., 2003; Wooding et al., 2004). The AAI and PVI haplotypes are rarely observed outside of populations of African descent (Wooding et al., 2004). Those who are PAV-homozygous are most sensitive to the taste of PTC/PROP, those who are AVI-homozygous are least sensitive, and those who are PAV/AVI have intermediate sensitivity (Bufe et al., 2005; Duffy et al., 2004). The AAI, AAV, and PVI haplotypes also are thought to have intermediate PTC/PROP sensitivity (Bufe et al., 2005; Kim et al., 2003).

Duffy et al. (2004) reported significant relationships among PTC gene haplotypes, PROP taste sensitivity, and alcohol consumption. In a study of nonalcoholic participants primarily of European ancestry, AVI homozygotes consumed more alcohol than did PAV/AVI heterozygotes, who in turn consumed more than did PAV homozygotes. However, PROP taste sensitivity was a more robust predictor of alcohol consumption than was PTC diploid haplotype (or diplotype, the combination of alleles from a pair of chromosomes). Further, PROP taste sensitivity was related independently to both PTC diplotype, on the one hand, and to the density of fungiform papillae on the anterior tip of the tongue, on the other hand, suggesting multiple genetic determinants of the PTC/PROP phenotype.

The present study attempted to determine whether PTC gene polymorphisms are associated with decreased incidence of cigarette smoking. A priori predictions were made with respect to the PAV and AVI haplotypes. Specifically, we predicted that, among the possible diplotypes of these two haplotypes, smoking incidence would be lowest in PAV homozygotes, highest in AVI homozygotes, and intermediate in PAV/AVI heterozygotes. No a priori

predictions were made for the AAV, AAI, and PVI haplotypes. Specific predictions were made for the PAV and AVI haplotypes but not the other haplotypes because (a) PAV and AVI are thought to represent opposite ends of the PTC/PROP taste sensitivity continuum for the PTC gene, (b) the PAV/AVI heterozygote permits a test of an intermediate phenotype without introducing confounds possibly associated with other haplotypes, (c) PAV and AVI are the most common haplotypes, which means the statistical power of tests of predictions made regarding them should be greatest, and (d) the predictions are consistent with the recent finding of a similar relationship between PAV and AVI haplotypes and alcohol consumption (Duffy et al., 2004).

Further, we examined the relationship between PTC gene polymorphisms and the importance that smokers assign to the taste of cigarettes as a motive for smoking. Smokers routinely rate the taste of cigarettes as an important motive for smoking (Brandon & Baker, 1991; Piper et al., 2004). In addition, laboratory research by Perkins and colleagues (2001) shows that cigarette taste can influence hedonic ratings of smoked cigarettes as well as their self-administration. Specifically, we evaluated the relationship between PTC diplotype and scores on the taste/sensory processes scale of the Wisconsin Inventory of Smoking Dependence Motives–68 (WISDM-68; Piper et al., 2004). The WISDM-68 comprises 13 scales designed to assess different motives that have been empirically and theoretically linked to dependence on tobacco cigarettes. As with smoker incidence and for the same reasons, a priori predictions were made for the PAV and AVI haplotypes but not the other haplotypes. Specifically, we predicted that smokers with the PAV homozygote would rate the taste of cigarettes as a less important reason for smoking than would smokers with the AVI homozygote, and we predicted that ratings by smokers with the PAV/AVI heterozygote would be intermediate. We predicted that, of the 13 WISDM-68 scales, only taste/sensory processes would be related to PAV and AVI haplotypes.

Method

Research participants

All research participants were of European descent. Because of concerns about population stratification, we did not combine data across race or ethnic groups, and the frequency of persons of non-European descent in the sample recruited was too low to permit separate analyses of their data. Consequently, persons of non-European ancestry were not included in this report.

Nonsmokers ($n=194$) were recruited from the general community via flyers and television advertisements in Milwaukee, Wisconsin. They reported they had not smoked more than 100 cigarettes in their lifetime. Smokers ($n=386$) were recruited for DNA substudies from two large randomized double-blind placebo-controlled smoking cessation trials. Smokers were recruited via flyers, print, radio, and television advertisements in Milwaukee and Madison, Wisconsin. We used more advertisement media to recruit participants for the smoking cessation trials because of the larger sample size and the study requirements; however, the majority of smokers were recruited via television advertisements. All were current smokers who smoked at least 10 cigarettes/day. Study procedures were approved by the institutional review boards at the University of Wisconsin and the University of Utah.

Genotyping

Based on Kim et al. (2003), we defined PTC gene haplotypes by identifying SNPs at base pairs 145, 785, and 886 on the PTC gene. SNPs were determined by the University of Utah Sequencing Core Facility. This facility uses the ABI3730 96-capillary sequencer, which employs fluorescent DNA sequencing technology. Primers for the three SNPs that constitute the haplotypes are as follows: 145 F=5' tgggtggcaaccaggctctt 3', 145 R=5' ctcaggaacagcagtc-catgc 3', 785 F=5' gtggtctgtgctctcttcccta 3', 785 R=5' tcgcgccacagaatcagtag 3', 886 F=5' tcattctgtg-ccctactgatt 3', and 886 R=5' gcctgtggtcggctcttac 3'. This gene contains one exon. All primers are located in the exon, with the exception of 145F, which is located 54 base pairs upstream from the ATG start codon. Polymerase chain reaction was performed with Applied Biosystems TaqMan Mastermix in 25 μ l solution of the following components: 50 ng of DNA (5 μ l), 20 pmol Primer F, 20 pmol Primer R, 5 pmol Probe FAM, 5 pmol Probe VIC, 12.5 μ l Applied Biosystems TaqMan Mastermix, HPLC water to a total volume of 25 μ l. All three polymorphisms were found to be in Hardy-Weinberg equilibrium in both the smoker and the control samples.

Assessment of smoking motives

All smokers were administered the WISDM-68 (Piper et al., 2004), which is a 68-item self-report measure. Each item is rated on a seven-point scale (1="not at all true of me", 7="extremely true of me"), and the 13 scale scores are the mean ratings of scale items. Thus the higher the scale score, the stronger the respondent is endorsing the latent variable underlying the scale. We used the WISDM-68

taste/sensory properties scale to assess the importance of the taste of cigarettes as a reason for smoking. Four of the six taste/sensory properties scale items ask about taste ("I enjoy the taste of cigarettes most of the time," "The flavor of a cigarette is pleasing," "Most of my daily cigarettes taste good," and "Some of the cigarettes I smoke taste great"), and the other two ask about other sensory properties ("I love the feel of inhaling the smoke into my mouth" and "I enjoy the sensations of a long, slow exhalation of smoke").

Alcohol intake

Alcohol consumption during the 30 days prior to beginning the study was assessed. If participants indicated they had had at least one drink in the previous 30 days, they were asked on how many of the last 30 days they had drunk alcohol (frequency) and how many drinks they usually drank when they did drink (quantity). Alcohol intake was taken to be frequency times quantity. If participants denied drinking alcohol at all during the previous 30 days, alcohol intake was set to 0.

Data analyses

Chi-square tests were used to evaluate the association between PTC diplotype and categorical variables. If an association was found across genders, then the analysis was repeated for females and males separately to ensure that the observed association was not gender specific.

Possible relationships between PTC diplotype and WISDM-68 scales were evaluated using an analysis of variance (ANOVA) design in which the scale score was the dependent variable and diplotype, gender, and the diplotype \times gender interaction effects were the independent variables. This design controls for possible confounding effects associated with gender. If a significant diplotype effect was found, pairwise comparisons of diplotype least squares means were made using Tukey post-hoc tests. Each of the 13 WISDM-68 scales was evaluated to determine whether the possible relationship with taste/sensory processes was specific to that scale. All statistical tests were computed using SYSTAT version 10.2.

Results

Following genotyping, we found 13 participants to have rare haplotypes (two had an AAI haplotype and 11 had a PVI haplotype). The AAI and PVI haplotypes were too infrequent in our sample to permit their inclusion in the chi-square analyses. As a result, nine female control subjects, one female smoker, two male control subjects, and one male

Table 1. Demographic variables by smokers ($n=384$) and nonsmokers ($n=183$).

| Variable | Smokers | | Nonsmokers | |
|---------------------|--------------------|------|--------------------|------|
| | Number of subjects | % | Number of subjects | % |
| Married | 139 | 36.2 | 66 | 36.1 |
| Education >12 years | 270 | 70.3 | 154 | 84.2 |
| Wage earner | 196 | 51.0 | 106 | 57.9 |
| Female | 212 | 55.2 | 128 | 69.9 |

smoker were excluded from all data analyses. Thus 384 smokers and 183 control subjects constituted the final sample of 567 research participants.

Smokers smoked a mean of 22.1 cigarettes/day ($SD=9.1$). We found no difference in the mean age of smokers (41.4 years, $SD=11.6$) and control subjects (41.3 years, $SD=16.0$). The groups did not differ in median income range (US\$35,000–\$49,999). Smokers reported drinking more alcoholic drinks in the previous 30 days (16.8 drinks, $SD=27.7$) than did nonsmokers (7.3 drinks, $SD=10.6$), $t(448)=2.745$, $p=.006$. Categorical demographic characteristics of smokers and control subjects are shown in Table 1. We found no difference between groups in either the percentage who were married or the percentage who were wage earners. A higher percentage of control subjects (84.2%) than smokers (70.3%) had more than 12 years of education, $\chi^2(1, N=567)=12.588$, $p=.001$. Further, we found a higher percentage of females among control subjects (69.9%) than among smokers (55.2%), $\chi^2(1, N=567)=11.212$, $p=.001$.

To rule out possible confounds between demographic variables and diplotype frequency, we conducted separate chi-square analyses of diplotype frequency by marital status, employment status, education level, and gender. We found no significant associations between these variables and PTC

Table 3. Smoking frequency by gender and presence of the AAV haplotype.

| Gender | Group | Diplotype group | |
|----------------------------|---------|-----------------|--------|
| | | AAV/* | No AAV |
| Female | Control | 21 | 107 |
| | Smoker | 18 | 194 |
| | Total | 39 | 301 |
| Smoker percentage | | 46% | 64% |
| Male | Control | 9 | 46 |
| | Smoker | 11 | 161 |
| | Total | 20 | 207 |
| Smoker percentage | | 55% | 78% |
| Combined smoker percentage | | 49% | 70% |

Note. AAV/*, sum of the PAV/AAV and AVI/AAV diplotypes; No AAV, sum of the PAV/PAV, PAV/AVI, and AVI/AVI diplotypes.

diplotype, and an ANOVA showed no age difference across PTC diplotypes. Further, we found no difference across PTC diplotypes in number of alcoholic drinks consumed in the previous 30 days.

The predicted protective effect of the PAV haplotype relative to the AVI haplotype was tested across the PAV homozygote, PAV/AVI heterozygote, and AVI homozygote. Across genders, we found no significant association between smoker frequency and these three diplotypes (Table 2). Smoker incidence trended in the predicted direction among males but was not reliably associated with PAV and AVI diplotypes.

Inspection of smoker frequencies in Table 2 suggests the AAV haplotype may be a smoking protective factor. To test this post-hoc hypothesis, we compared the incidence of smokers in the AVI/AAV and PAV/AAV diplotypes combined with the incidence across AVI/AVI, PAV/AVI, and PAV/PAV diplotypes combined (Table 3). Smokers were less prevalent across genders among participants with the AAV haplotype (49%) than among those without it (70%), $\chi^2(1, N=567)=10.392$, $p=.001$. Separate tests

Table 2. PTC diplotype frequency by gender and smoker status with the percentage of each diplotype in the total sample (including the 13 instances of AAI and PVI haplotypes) and the percentage of smokers within each diplotype.

| Gender | Group | Diplotype | | | | | Total |
|----------|----------------------|-----------|---------|---------|---------|---------|-------|
| | | PAV/PAV | PAV/AVI | AVI/AVI | PAV/AAV | AVI/AAV | |
| Female | Control | 18 | 53 | 36 | 8 | 13 | 128 |
| | Smoker | 32 | 97 | 65 | 7 | 11 | 212 |
| | Total | 50 | 150 | 101 | 15 | 24 | 340 |
| | Diplotype percentage | 14% | 43% | 29% | 4% | 7% | 97% |
| | Smoker percentage | 64% | 65% | 64% | 47% | 46% | 62% |
| Male | Control | 9 | 27 | 10 | 3 | 6 | 55 |
| | Smoker | 23 | 81 | 57 | 6 | 5 | 172 |
| | Total | 32 | 108 | 67 | 9 | 11 | 227 |
| | Diplotype percentage | 14% | 47% | 29% | 4% | 5% | 99% |
| | Smoker percentage | 72% | 75% | 85% | 67% | 45% | 76% |
| Combined | Diplotype percentage | 14% | 44% | 29% | 4% | 6% | 98% |
| | Smoker percentage | 67% | 69% | 73% | 54% | 46% | 68% |

by gender were significant for both genders: For males, $\chi^2(1, n=227)=5.154, p=.023$, and females, $\chi^2(1, n=340)=4.925, p=.026$.

The hypothesized relationship between the importance of the taste of cigarettes as a motive for smoking and the PAV and AVI haplotypes was supported. We found a significant difference in mean ratings of the WISDM-68 taste/sensory processes scale across the PAV/PAV, PAV/AVI, and AVI/AVI diplotypes, $F(2, 348)=3.303, p=.038$. The gender and gender \times diplotype interaction effects were not significant. Tukey post-hoc comparisons indicated a significantly lower rating by PAV homozygotes than by AVI homozygotes, $p=.031$, with the PAV/AVI heterozygotes not significantly different from either of the two homozygotes (see Table 4 for means and standard deviations).

The only other WISDM-68 scale with which PAV and AVI was associated was the cue exposure-associative processes scale, $F(2, 348)=4.874, p=.008$. This scale is designed to measure smoking motivation in response to smoking cues. Sample items include "My life is full of reminders to smoke" and "There are particular sights and smells that trigger strong urges to smoke." Tukey post-hoc tests indicated lower cue-exposure ratings by PAV homozygotes than by AVI homozygotes, $p=.009$, with the PAV/AVI heterozygotes not significantly different from either of the two homozygotes (Table 4). In addition to a significant diplotype effect, we found a significant gender effect, $F(1, 348)=5.637, p=.018$, but the diplotype \times gender effect was not significant. Females rated this scale more highly ($M=4.717, SD=1.237$) than did males ($M=4.483, SD=1.206$). The relationship between the three PAV-AVI diplotypes and cue exposure is not independent of the relationship between these diplotypes and taste/sensory processes. Among participants with the PAV-AVI diplotypes, the two scales are correlated, $r(353)=.472, p=.001$. In an analysis of covariance in which cue exposure was the dependent variable, taste/sensory processes was the covariate, and diplotype, gender, and gender \times diplotype were the independent variables, we found a large effect related to taste/sensory processes, $F(1, 347)=96.885, p=.001$, but no significant effect related to diplotype.

Based on the finding that the AAV haplotype is associated with a lower incidence of smoking, we conducted a post-hoc test of the relationship between the taste/sensory processes scale and the AAV

haplotype, with gender and gender \times haplotype effects included in the ANOVA. We found no significant difference in mean taste ratings made by participants with the AAV haplotype ($M=4.121, SD=1.484$) and those without ($M=4.153, SD=1.357$).

Discussion

The present results are consistent with the hypothesis that polymorphisms in the PTC gene protect against cigarette smoking, as suggested by earlier reports of an inverse relationship between the ability to taste PTC and the likelihood of being a cigarette smoker (Enoch et al., 2001; Kaplan & Glanville, 1964). However, the specific haplotype associated with lowered incidence of smoking was not the haplotype predicted to be a protective factor. PAV (a PTC/PROP "taster" haplotype) was predicted to be associated with a lower incidence of smoking relative to AVI (a PTC/PROP "nontaster" haplotype), but no such difference was observed. Instead, AAV (a PTC/PROP "intermediate taster" haplotype) was observed to protect against smoking. Given that there was no a priori basis for predicting a protective effect for AAV, and given the risk of Type I errors in genetic association studies, this finding must be viewed with caution until it can be replicated. If the finding is replicated, then an explanation of why AAV is associated with a lower incidence of smoking must await further research.

The results confirm the prediction that the PAV and AVI haplotypes are differentially associated in smokers with the importance of the taste of cigarettes as a motive for smoking. This finding is consistent with the reported relationship between the PAV and AVI haplotypes and alcohol consumption in social drinkers (Duffy et al., 2004). The AAV haplotype was not associated with the ratings of the taste of cigarettes as a smoking motive.

The association of AAV with smoking and the relationships of PAV and AVI with smoking motivation were independent of gender. This gender independence is important because the sample contained a higher proportion of smokers among males than females. Thus our findings do not suggest mechanisms that could account for gender differences in the reinforcing value of cigarette smoke (Perkins et al., 2001).

Table 4. WISDM-68 scale scores (means and standard deviations) by PAV-AVI diplotype.

| WISDM-68 scale | PAV/PAV (n=54) | | PAV/AVI (n=176) | | AVI/AVI (n=122) | |
|--------------------------|----------------|-------|-----------------|-------|-----------------|-------|
| | Mean | SD | Mean | SD | Mean | SD |
| Taste/sensory properties | 3.809 | 1.528 | 4.112 | 1.331 | 4.364 | 1.289 |
| Cue exposure | 4.175 | 1.524 | 4.614 | 1.193 | 4.771 | 1.138 |

The protective effect of AAV was substantial (i.e., more than a 20% reduction in smoker frequency), but the impact of this protective effect in the general population is likely to be modest because of the low incidence of the AAV haplotype. The estimated smoking reduction in a population would be the product of the protective effect of AAV and the prevalence of the AAV haplotype in the population. The AAV haplotype was identified in 10% of our European-descent sample, but other studies have found the incidence of AAV among persons of European descent to be 3%–5% (Kim et al., 2003; Wooding et al., 2004). Thus the expected reduction in smoker frequency among European descendants related to AAV would be no more than 2%. Because the prevalence of AAV among persons of African descent is 3%–4% (Kim et al., 2003; Wooding et al., 2004), the expected protective effect of AAV among African descendants would be less than 1%. The AAV haplotype has not been observed in other world populations (Wooding et al., 2004); thus, the protective effect of AAV may not occur at all in those populations.

The fact that the taste/sensory processes scale was associated with PAV and AVI suggests this scale is measuring, in part, a motivational process in smokers that is related to the biology of bitter taste perception. This association needs to be replicated in independent samples. The cue exposure–associative processes scale also was significantly related to PAV and AVI, but that relationship was not independent of the cue-exposure scale's correlation with the taste/sensory processes scale.

Taste is not a single-gene trait, and the taste of cigarette smoke is the result of its many constituents, not all of which have a bitter taste. Future research on the role of taste as a protective factor for smoking and its effects on smoking motivation should investigate other taste genes and other flavors present in cigarette smoke. The role of olfactory stimuli in cigarette smoke also should be explored. The present study began with the PTC gene because the PTC/PROP taste phenotype has been reported to be a smoking protective factor (Enoch et al., 2001; Kaplan & Glanville, 1964) and because the PTC gene recently has been reported to predict alcohol consumption (Duffy et al., 2004), but those reasons do not imply that the PTC gene will prove to be the taste gene most important for smoking.

Nicotine dependence is likely to be the result of many genes and complex environmental effects, and different genetic factors may be in play during the initiation of smoking, smoking persistence, and smoking cessation (for reviews, see Crabbe, 2002, and Munafò, Johnstone, Murphy, & Walton, 2001). Understandably, most research on the genetics of nicotine addiction has focused on genes thought to

be involved in nicotine metabolism, drug reinforcement, affect regulation, personality, and psychiatric comorbidity. The present research suggests that genetic factors underlying the perception of the taste of cigarettes should be examined as part of a comprehensive analysis of the genetic determinants of smoking.

Acknowledgments

This study was supported by National Institute on Drug Abuse grant DA13981-01 and National Cancer Institute grant CA84724.

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