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Association of catechol-O-methyltransferase with smoking cessation in two independent studies of women

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Abstract

Objectives and methods—The Val108/158Met polymorphism in the gene that encodes COMT, a dopamine metabolizing enzyme, results in a three- to four-fold reduction in COMT activity. To determine if the lower activity Met allele of COMT was associated with smoking cessation in women, we used two independent studies: a population-based case-control study and a nicotine replacement clinical trial.

Results— In the case-control study, women with two Met alleles were significantly more likely to be ex-smokers than current smokers [OR = 1.82, 95% CI (1.05, 3.17), $P = 0.03$]. In the nicotine replacement clinical trial, among women, the Met/Met genotype was associated with a higher probability of smoking cessation based on both point prevalence and prolonged abstinence outcomes [OR= 2.96, 95% CI (1.07, 8.14), $P = 0.04$; OR= 3.23, 95% CI (1.13, 9.20), $P = 0.03$, respectively].

Conclusions— This first report of a significant association between COMT Val108/158Met and smoking cessation suggests that COMT variation has an effect on smoking behavior in women.

Keywords

smoking cessation; COMT; women; tobacco dependence; pharmacogenetics

Introduction

Cigarette smoking is a serious public health problem, with an estimated 23% prevalence among U.S. adults in 2002 [1]. Even with the most effective smoking cessation interventions, few smokers maintain long-term abstinence [2]. Twin studies suggest that up to 54% of the variance in smoking cessation is attributable to inherited factors [3]. Evidence suggests that genes in the dopamine reward pathway may influence smoking cessation [4].

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Nicotine stimulates release of dopamine from neurons in the ventral tegmental area, an action thought to underlie its rewarding effects [5,6]. Catechol-*O*-methyltransferase (COMT) is the primary enzyme involved in the degradation and inactivation of the neurotransmitter dopamine [7]. Different processes in the brain metabolize dopamine so that it is no longer available for receptor stimulation. These processes include oxidation by monamine oxidase (MAO) in presynaptic nerve terminals and *O*-methylation by COMT in glial and neuronal cells. COMT protein and activity is widely distributed in the brain [8,9]. COMT mRNA has been demonstrated in different parts of the brain, with levels higher in neuronal rather than glial cells of the prefrontal cortex, a lesser amount in the striatum, and the least in the midbrain [10]. An important role for COMT is identified through the study of COMT-deficient mice, where dopamine levels are significantly high in total brain tissue in general, and the striatum and hypothalamus in particular [11]. Other studies of COMT-specific inhibitors show the importance of COMT prefrontal cortex performance [12]. Thus, the gene that encodes COMT (denoted *COMT*) is a plausible candidate for genetic studies of nicotine dependence and smoking cessation.

Several polymorphisms for *COMT* have been described, with varying frequencies in the population (<http://snp500cancer.nci.nih.gov/snp1ist.cfm>). There is a G to A transition in codon 158/108 of *COMT* (rs4680) that converts a Val high-activity allele to a Met low-activity allele, resulting in a three- to four-fold reduction in COMT activity [9]. This polymorphism significantly correlates with COMT protein abundance and activity, but not mRNA levels, in the prefrontal cortex, a brain region thought to be particularly important in COMT effects on cognition and neuropsychiatric conditions [13,14]. It is also found to be associated with tyrosine hydroxylase gene expression, which is important in dopamine metabolism [13]. The importance of this low-activity allele is highlighted by data showing an effect on phenotypes of memory and other executive functions [15]. The Val allele is associated with higher metabolic activity of COMT which presumably leads to lower synaptic dopamine levels in the prefrontal cortex than in persons with the Met allele.

Several lines of evidence suggest that COMT activity may vary by sex because of the effects of estrogen metabolism. COMT metabolizes catechol estrogens to estrone. Estrogen is a regulator of *COMT* promoter activity and COMT activity is lower in women compared to men [7,18]. Thus, the effect of *COMT* genotype on smoking cessation may vary between women and men given the sex-specific differences in COMT activity. Given COMT's role in dopamine metabolism, and the role of the dopamine reward pathway in nicotine dependence, we examined data from two independent studies of women smokers for an association between the *COMT* Val108/158Met single nucleotide polymorphism (SNP) and smoking cessation.

Methods

We examined the association between *COMT* Val108/158Met and smoking cessation in 785 women from a control group participating in two concurrent population-based case-control studies of breast and endometrial cancer, known as WISE (Women's Insights and Shared Experiences). Eligible female participants, aged 50–79, with no history of cancer, were selected by random-digit dialing if they resided in one of nine counties around the Philadelphia metropolitan area. Women who were classified as ever regular smokers (defined as having smoked at least five cigarettes per day for at least 1 year) and who provided a buccal swab sample for DNA extraction were included for analysis. Women who reported having stopped smoking prior to study ascertainment were considered former regular smokers; women who did not report stopping smoking were considered current regular smokers. Never smokers were excluded from these analyses.

To determine if we could replicate our results, we genotyped 290 women participating in a randomized, open-label smoking cessation clinical trial comparing alternate forms of nicotine replacement therapy (NRT) [16]. The participants, who were treatment seeking smokers, were enrolled at Georgetown University (Washington, DC) and the University of Pennsylvania (Philadelphia, Pennsylvania) from February 2000 through August 2003. Women were eligible for inclusion in our analysis if they were current cigarette smokers, 18 years of age or older, smoked 10 or more cigarettes per day for the previous 12 months, and gave a blood sample for DNA extraction. Subjects were randomized to transdermal nicotine versus nicotine nasal spray for smoking cessation, and received standardized behavioral group counseling and stress management. Nicotine replacement therapy was delivered for the standard period of 8 weeks, and participants were advised to start treatment on the morning of the target quit date. Abstinence from smoking was assessed and biochemically confirmed at the end of 8 weeks of treatment (8 weeks after target quit date) and 6 months after the target-quit date. Two measures of quit rates were obtained: point prevalence of smoking cessation (defined as 7 days of continuous abstinence immediately before end of follow-up, verified by a carbon monoxide reading ≤ 10 parts per million) and prolonged abstinence from smoking, those individuals who did not have a smoking relapse, which was defined as 7 consecutive days of smoking at any point between the target-quit date and follow-up.

Genomic DNA was genotyped for the Val108/158Met polymorphism in *COMT* using identical assays designed by Applied Biosystems Assay-By-Design (ABI, Foster City, California, USA). PCR amplifications in 384-well plates were completed according to manufacturer's recommended protocols in MJ Research tetrad thermal cyclers (MJ Research Inc., Waltham, Massachusetts). After PCR, microtiter plates were transferred to the ABI 7900 HT Sequence Detection System (ABI). End-point fluorescence levels of 6FAM and VIC were measured automatically in each well using the SDS 2.1 manufacturer's custom software (ABI). Both studies obtained IRB approval at each of the participating institutions.

Unconditional logistic regression was used to examine the relationship between *COMT* genotype and each of the smoking cessation outcome measures. To be consistent, models in both studies adjusted for the following covariates: age, body mass index (BMI), education (college graduate: yes/no), and alcohol consumption. These covariates were found to be significant predictors of smoking cessation or were suspected, *a priori*, to be potential confounders of the *COMT* genotype and smoking cessation association. In addition, the NRT trial analysis included research site and treatment group as covariates. Given that literature has reported the *COMT* Val108/158Met polymorphism with both codominant and recessive effects on functional activity [17,18], we chose to assess the effect of each individual *COMT* genotype (i.e. Val/Val, Val/Met, Met/Met) on smoking cessation in our analysis, rather than assuming a particular genetic model. *COMT* alleles were also considered in an ordinal fashion in order to compute a test for trend with increasing number of Met alleles. Separate models of smoking cessation were estimated for women of European and African ancestry in the WISE study because of the different allele frequencies in these groups. For the NRT trial, descriptive statistics are presented for both groups; however, due to the smaller number of women of African ancestry in the trial, we were not able to use multivariate regression to estimate the effect of *COMT* on smoking cessation in this group.

Results

Descriptive statistics and genotype frequencies of the *COMT* polymorphism for both studies are presented in Table 1. In both studies, there were significant differences ($P<0.05$) between women of European and African ancestry in BMI, alcohol consumption and education. In addition, the Met/Met genotype was found to be less frequent in women of African ancestry

in both studies. The distribution of *COMT* genotypes was similar in both studies. The allele frequencies among women in both studies were in Hardy–Weinberg equilibrium.

Multivariate logistic regression was used to examine the association between *COMT* genotype and the probability of being a former regular smoker (Table 2). In the WISE study, stepwise regression indicated that age and graduating from college were positively associated with smoking cessation among women of European ancestry ($P=0.009$ and $P<0.0001$, respectively), while age was the only significant covariate in the model for women of African ancestry ($P<0.0001$). After adjusting for age, education, BMI, and alcohol consumption, women of European ancestry with the Met/Met genotype were more likely than women with the Val/Val genotype to be former smokers (OR=1.82, 95% CI: 1.05–3.17). A significant dose-response relationship was found between smoking cessation and the number of Met alleles in a woman's genotype ($P=0.03$). The association between *COMT* genotype and former smoking was not present among women of African ancestry in this study.

Among 178 women of European ancestry in the NRT smoking cessation clinical trial, those homozygous for the Met allele were significantly more likely than women with Val/Val genotype to be abstinent from smoking at end of treatment (8 weeks after the target quit date) (Table 2). The Met/Met genotype was associated with both the point prevalence of smoking cessation (OR=2.96, 95% CI: 1.07–8.14) and prolonged abstinence (OR=3.23, 95% CI: 1.13–9.20). The probability of smoking cessation increased significantly with the number of Met alleles for individuals who stopped smoking as measured by both point prevalence ($P=0.04$) and prolonged abstinence ($P=0.03$), indicating that having more Met alleles increases the ability to achieve smoking cessation. For the NRT data, study site was the only significant covariate for smoking cessation aside from *COMT* genotype. *COMT* genotype was not significantly associated with either smoking cessation phenotype among the women of African ancestry when examined in an unadjusted analysis (data not shown).

Examining the effect of *COMT* genotype on smoking cessation in men was not a primary focus of our study, since we only had access to data on males in the NRT study. When examined, however, we did not find an association between *COMT* genotype and smoking cessation in the men from the NRT trial for either the point prevalence or prolonged abstinence measures (For the Met/Met genotype, OR=1.08, 95% CI: 0.53, 2.18 and OR=1.09, 95% CI: 0.54, 2.20, respectively).

Discussion

The results of these two independent studies provide consistent support for an association between the Met/Met genotype of *COMT* and smoking cessation among women of European ancestry. Because *COMT* accounts for the majority of the metabolic degradation of dopamine in the brain [7], the diminished *COMT* activity associated with the Met allele could result in the maintenance of dopamine levels and function in the brain. Higher levels of dopamine in smokers with one or more Met alleles might facilitate smoking cessation by minimizing the phasic effects of nicotine from smoking on dopamine release [19], thereby reducing positive reinforcement from smoking relapse episodes. It is also possible that higher levels of dopamine activity minimize abstinence-induced withdrawal symptoms [20].

We observed the association between *COMT* genotype and smoking cessation in our samples of women of European descent but not in women of African descent. There are several possible reasons for this difference. First, studies have found African-Americans and Africans have a lower frequency of the Met/Met genotype than other populations [21]. *COMT* activity has also been shown to be lower in the erythrocyte cells of African-Americans than in white Americans [22]. If the protective allele is less common in persons of African ancestry, the power to detect

a significant association will be greatly reduced, even for an odds ratio of equal magnitude. Given that our sample of women with African ancestry was not as large as the sample of women with European ancestry, our ability to find a significant association in this group was greatly diminished. However, the magnitude of the odds ratio for the Met/Met genotype among women with African ancestry was also reduced, relative to the odds ratio among women of European ancestry. Second, this reduced odds ratio suggests that it is possible that certain environmental factors involved in the complex behavior of smoking cessation might confound the relationship between *COMT* and smoking cessation in one population but not in another. We adjusted for covariates that we suspected could be potential confounders (age, education, BMI and alcohol use) in our analyses, so we do not believe that these confounders are likely to explain the ethnic difference found; however, other potential unmeasured confounders (e.g. diet, exercise, other medication use) could account for these differences.

In the NRT trial, we found that *COMT* genotype was significantly associated with smoking cessation in women but not men. Since only women were included in the WISE study, we were not able to replicate this finding in men using the WISE data. There is some evidence, however, that individual differences in *COMT* activity may vary by sex because of the effects of estrogen metabolism. *COMT* is involved in estrogen metabolism, breaking down catechol estrogens to estrone. Estrogen is a regulator of *COMT* promoter activity and *COMT* activity is lower in the blood [23] and in the brain [14] of women compared to men. Thus, the effect of *COMT* genotype on smoking cessation may vary biologically between women and men given the sex-specific differences in *COMT* activity.

The relationship between this *COMT* polymorphism and smoking has been examined previously in an English population. In two reports, the authors found no significant association between *COMT* Val108/158Met and cigarette consumption [24], or smoking cessation [25]. In these studies, the relationship between *COMT* and smoking cessation was not examined separately in women. This is the first report on *COMT* and smoking behavior in a clinical trial where smoking cessation was biochemically verified. In addition, a recessive model for the Val allele was assumed, where a Val/Val genotype was considered the high-risk genotype for smoking initiation. Since we found a significant effect in women only with the homozygous Met/Met genotype, it is possible that previous studies did not find an association because they analyzed the heterozygous and homozygous Met genotypes together.

There is no evidence to date that population stratification affects the results of association studies involving populations of European descent [26]. Our analyses were stratified by race to control for potential confounding due to ethnicity. The NRT trial evaluated population substructure by genotyping markers unlinked to *COMT* using the method of Pritchard *et al.* [27], and found no evidence of population substructure in either ethnic group studied (results not shown). While it is unlikely that population stratification has influenced the results in women of European ancestry, further research is needed to determine if *COMT* affects smoking cessation in women of African ancestry.

It should be noted that while we found similar results in the two studies reported here, the merits and limitations of each study are different. In the WISE study, information about smoking cessation was obtained through self-reported answers to a questionnaire. Because of potential biases in retrospectively collected self-reported data, such self reports may not accurately reflect a person's current smoking history or habits. However, all the women included in the WISE study were controls drawn from within a case-control study, so there is little potential for differential recall bias in our analysis. The WISE study did, moreover, have a large sample size which was randomly selected from the Philadelphia area population. The NRT trial was designed to estimate smoking cessation rates in groups of treatment seeking smokers randomized to receive alternate forms of nicotine replacement therapy. In this

smoking cessation trial, self-reports of smoking cessation were biochemically verified using carbon monoxide readings. The NRT trial also assessed participant's levels of nicotine dependence, as measured by the Fagerstrom Test for Nicotine Dependence. Although this study was able to follow participants and biologically verify abstinence from smoking, it was limited by a smaller sample size that precluded a sufficiently powerful analysis for the sample of women with African ancestry.

Our results suggest that *COMT* Val108/158Met genotype and by inference, its influence on other factors involved in dopamine metabolism, may contribute to the interindividual variability among women in the ability to quit smoking. Future research should examine mechanisms by which *COMT* variation could influence smoking behavior, including effects on other neurotransmitters. These studies could lead to biologically driven pharmacogenetic interventions for smoking cessation.

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Table 1

Frequency distribution of descriptive characteristics for two studies

	WISE Study		Nicotine Replacement Trial	
	Women of European ancestry (N = 541)	Women of African ancestry (N = 241)	Women of European ancestry (N = 178)	Women of African ancestry (N = 112)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Continuous variables				
Age	61.8 (7.9)	60.3 (7.6)	47.2 (12.2)	44.6 (7.9)
Body mass index	23.6 (4.2)	26.0 (5.4)	28.2 (5.4)	30.0 (7.0)
Alcoholic drinks consumed per week	N/A	N/A	5.7 (6.9)	2.5 (4.8)
Nicotine dependence (FTND)	N/A	N/A	5.2 (2.2)	5.4 (1.7)
Discrete variables	N (%)	N (%)	N (%)	N (%)
College graduate				
Yes	148 (27)	30 (12)	81 (46)	37 (33)
No	393 (73)	211 (88)	97 (54)	75 (67)
Research site				
U. of Pennsylvania	541 (100)	241 (100)	115 (65)	84 (75)
Georgetown U.	0 (0)	0 (0)	63 (35)	28 (25)
Treatment group				
Spray	N/A	N/A	99 (56)	55 (51)
Patch			79 (44)	57 (49)
Do you drink alcohol regularly?				
Yes	404 (75)	53 (22)	N/A	N/A
No	137 (25)	188 (78)		
Regular smokers				
Former	381 (70)	124 (51)	N/A	N/A
Current	160 (30)	117 (49)		
Point prevalence at EOT				
Yes	N/A	N/A	51 (29)	42 (38)
No			127 (71)	70 (62)
Prolonged abstinence at EOT				
Yes	N/A	N/A	47 (26)	41 (37)
No			131 (74)	71 (63)
COMT genotype				
Val/Val	125 (23)	102 (42)	40 (23)	52 (46)
Val/Met	291 (54)	114 (47)	90 (51)	51 (46)
Met/Met	127 (23)	26 (11)	48 (27)	9 (8)
Hardy-Weinberg equilibrium test <i>P</i> -value	0.09	0.48	0.86	0.47

Logistic regression model results for association between COMT genotype and smoking cessation in WISE and NRT studies

Table 2

COMT Genotype	Odds ratio ^a (95% C.I.) for former regular vs. current regular smokers in WISE		Odds ratio ^b (95% C.I.) for smoking cessation phenotypes in NRT women of European ancestry	
	Women of European ancestry	Women of African ancestry	Point prevalence	Prolonged abstinence
Val/Val	1.0	1.0	1.0	1.0
Val/Met	1.45 (0.92, 2.30)	0.84 (0.47, 3.18)	1.26 (0.50, 3.22)	1.32 (0.50, 3.50)
Met/Met	1.82 (1.05, 3.17)	1.21 (0.48, 3.03)	2.96 (1.07, 8.14)	3.23 (1.13, 9.20)
Trend test				
P-value	0.03	0.98	0.04	0.03

^a Odds ratios are adjusted for age, body mass index, college graduate, and alcohol consumption.

^b Odds ratios are adjusted for age, body mass index, college graduate, alcohol consumption, research site and treatment group. Results were limited to participants of European ancestry due to the small number of women of African ancestry in the NRT trial who had Met/Met genotype.