Journal of Schizophrenia Research

Open Access

Austin Publishing Group

Research Article

Association between COMT Val158Met and Tobacco Smoking among Subjects with Schizophrenia and Bipolar Disorder: A Pilot Study

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Received: September 15, 2015; **Accepted:** November 05, 2015; **Published:** November 09, 2015

Abstract

Mentally ill patients are frequently tobacco smokers. This pilot study determined the association between the Catechol-O-Methyltransferase (COMT) Val158Met (rs4680) variants and smoking in patients with schizophrenia and bipolar disorder. The subjects were classified into current, former and never-smokers, and subdivided according to race gender and the genotype. The number of cigarettes smoked per day was used as the major parameter to assess their smoking behavior. Female schizophrenic smokers with the Met allele smoked significantly more cigarettes per day than males with the Val/Val genotype and schizophrenia. This significance was detected among African American, but not Caucasian patients with schizophrenia. Especially in female African Americans, the Met allele carriers smoked significantly more cigarettes per day than the Val/Val carriers. No significant association between the COMT genotypes and smoking status was found in patients with schizophrenia or bipolar disorder. In addition, no significant genotype and sex-related differences were found in Caucasians with schizophrenia or bipolar disorder. The results demonstrate that the COMT Met allele affects the number of cigarettes smoked per day, but this effect was sex, ethnic, and mental diagnosis-specific.

Keywords: Genetics; Schizophrenia; Bipolar disorder; Smoking; Number of cigarettes/day

Abbreviations

SCZ: Subjects With Schizophrenia; BP: Subjects with Bipolar Disorder; COMT: Catechol-O-Methyltransferase; SCID: Structured Clinical Interview for DSM-IV; DIGS: Diagnostic Interview for Genetic Studies; PCR: Polymerase Chain Reaction; DA: Dopamine

Introduction

Mental disorders and smoking are commonly co-morbid [1-5]. The Catechol-O-Methyltransferase (COMT) Val158Met variant (rs4680) has been considered as an important gene candidate for both mental disorders and tobacco smoking. Many studies evaluated the association between the COMT variant sand tobacco smoking cessation [6-10], smoking prevalence [11,12], risk of being heavy smoker [13] and nicotine dependence [14,15] in healthy control subjects (without mental disorders). However, less data are available for the association between the COMT polymorphism and mental disorders such as schizophrenia [16-18] and bipolar disorder [19-22].

COMT is a key enzyme involved in the metabolism of Catechol amines, especially Dopamine (DA) and nor epinephrine [23-26]. The Met variant has less enzyme thermos-stability which results in lower protein expression and lower enzymatic activity [27]. The differences induced by different COMT genotypes can be explained by the tonic-phasic DA hypothesis, with complexities and limitations including sex and phenotype differences, and a range of endogenous and environmental factors [28]. Also gender and ethnic specific genotype differences were reported in nicotine dependence among control subjects and patients with panic disorder, respectively [29,30]. The Met allele frequency differs in various ethnic groups, and it was reported to be 0.4-0.5 in Caucasians, 0.5 in South-West Asians, 0.2 in pure African populations [31-33]. Furthermore, the homozygous Met allele frequency is much lower in Kenyan population (0.1) than in Caucasians (0.3) or Southwest Asians (0.3) [34].

Our study aimed to confirm two hypotheses; 1) the COMT genotype alters tobacco smoking behavior, and 2) the genotype differences are influenced by subject's sex, race and type of mental illness.

Materials and Methods

Subjects

All participants (N=320) were recruited from local ambulatory care mental health clinics as described in a previous report [35]. They were included in a previous pharmacogenomic study related to atypical antipsychotics-associated metabolic complications [36]. Inclusion criteria were 1) DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or bipolar disorder I or II; 2) ≥18 years old; and 3) stable pharmacologic mental health treatment for at least 6 months. The exclusion criterion was inability to provide informed consent (assessed using a short questionnaire with key questions about the study including drug abuse). All subjects gave informed consent. The study protocol was approved by the University of Michigan Institutional Review Board. A trained assistant completed a research assessment using either the Structured Clinical Interview for DSM-IV (SCID) [37], or the

Citation: Hirasawa-Fujita M, Bly MJ, Ellingrod VL, Dalack GW, Pivac N and Domino EF. Association between COMT Val158Met and Tobacco Smoking among Subjects with Schizophrenia and Bipolar Disorder: A Pilot Study. J Schizophr Res. 2015; 2(3): 1017.

Table 1: Demographic data of all subjects.

Demographic Variable	SCZ	BP
Age ± SD	46.3±11.2	43.2±11.9
Sex		
Male	112	39
Female	60	77
Race		
Caucasian	98	95
African American	61	1
Other	13	8
Smoking History		
Current smoker	93	40
Former smoker	40	22
Never smoker	39	54
Overall pack year history±SD	21.1±22.5	17.2±21.1
Number of cigarettes per day±SD†	18.6±11.6	16.3±12.9

† Never smokers were excluded to calculate the number of cigarettes smoked per day. Pearson Chi-Square test indicates the distribution was significantly different between the diagnoses (p< 0.0001).
SCZ: Schizophrenia; BP: Bipolar Disorder

Diagnostic Interview for Genetic Studies (DIGS) [38] to confirm the psychiatric diagnosis. The euthymic state of the bipolar patients was assessed by the psychometric scales. This information was also confirmed by chart review when necessary. Different diagnostic instruments were used since subjects came from two different primary groups. The procedures used for gathering all other data were identical across subject groups. Subjects underwent a current and past medication history assessment, confirmed by a medical record review. Antipsychotic medication was determined using chlorpromazine equivalents [39]. A total of 320 patients with schizophrenia and bipolar disorder were recruited into this study and 28 patients with schizophrenia and 4 patients with bipolar disorder were excluded due to unavailable COMT genotype and smoking history.

Smoking status data collection

Life time smoking status was classified into current, former and never smokers. Current and former smokers provided information regarding the number of cigarettes smoked/day, age at initiation of smoking, and quit date (if applicable). The number of cigarettes smoked per day was reported by current and former smokers. For the former smokers, the number of cigarettes smoked per day was average number of cigarettes smoked in past.

Genotyping of the COMT Val 158Met (rs4680)

DNA was extracted from whole blood with Purgene kits (Qiagen, Valencia California). Genotyping of the COMT Val 158Met (rs4680) was done using polymerase chain reaction (PCR) and sequencing primers were designed by Pyrosequencing SNP Primer Design Version 1.01 software (http://www.pyrosequencing.com). The PCR were performed using One Taq 2X Master Mix with Standard Buffer (BiolabsInc) with the forward primer (5'-TCG TGG ACG CCG TGA TTC -3') and biotinylated reverse primer (5'- /5Bio/ CAC AGC CGG CCC TTT TTC -3') for COMT variant. The purity of PCR products were confirmed 1.8 % agarose gel electrophoresis. Pyrosequencing™ Technology was used to determine the genotype.

Statistical analysis

The COMT genotype was classified into two groups: Met allele carriers (the combined Val/Met and Met/Met genotypes), and the Val/Val genotype group. The number of cigarettes smoked per day was used as a major tobacco smoking parameter. Student's t tests and one-way ANOVA were used to compare the number of cigarettes smoked/day. The life time smoking status was used to assess smoking prevalence. Chi-square test was used to assess the Hardy-Weinberg equilibrium, smoking prevalence and population/genotype analyses. Linear regression model was used to elucidate contributions of factors including the COMT genotype, race, sex and diagnosis. All statistical analyses included current, former and never smokers. All of the medication groups were included in the analyses. The data were analyzed with IBM SPSS (Statistic Package for Social Sciences) statistics version 21 for Windows. A p value was considered significant if $p<0.05$. Statistical power (designated to be more than 0.800) and required sample size (N=273) with small effect size (w=0.2) for χ^2 test was calculated a priori by G* Power (http://www.gpower.hhu.de/).

Results

Population characteristics

A total of 288 smoking and nonsmoking patients diagnosed with schizophrenia (n=172) and bipolar disorder (n=116) participated in this study. All of the bipolar patients were at euthymic state which was assessed by psychometric scales at the moment of data acquisition. Their age ranged between 19-71 years (45.0±11.6). The majority of the subjects were Caucasians (67.0 %) followed by African Americans (25.7 %) and others including Asians, Indian Americans and Hispanics (7.3 %). The ethnic distributions were significantly different across diagnoses (χ^2 (2) =18.6, p< 0.0001). In the entire group, 133 (46.2 %) were current smokers, 62 (21.5 %) were former smokers and 93 (32.3 %) subjects had never smoked. The smoking status was significantly different between different diagnostic groups (χ^2 (2) =22.3, p< 0.0001). Those who were current and former smokers smoked an average of 17.8±12.0 cigarettes per day. Their average ± SD pack year history was 19.9±22.1 (Table 1). Summarizes the demographic data of all subjects.

COMT Val158Met genotype

The entire group of 288 subjects was genotyped for the COMT Val158Met polymorphism. There were 59 subjects (20.5%) with the Met/Met genotype, 135 subjects (46.9%) with the Val/Met genotype and 94 subjects (32.6%) with the Val/Val genotype. The Met genotype was the most common in Caucasian patients (χ^2=18.85, p<.001). All patients were subdivided according to schizophrenia and bipolar disorder. The genotype distributions were within the Hardy-Weinberg equilibrium (χ^2=0.68, 1.25, and 0.01, p value=0.71, 0.53, and 0.97 for total, schizophrenia and bipolar disorder, respectively). There were no significant sex differences in the genotype distribution (χ^2=0.10, 0.04, and 0.21, p value =0.76, 0.85, and 0.64 for total, schizophrenia and bipolar disorder, respectively) (Table 2). Summarizes the demographic data, racial distribution, the COMT Val158Met genotype distribution and number of cigarettes smoked per day.

Genotype, sex and ethnic differences in tobacco smoking

A linear regression model indicated that the COMT genotype,

Table 2: Demographic data of subjects with the COMT (Val[158]Met) genotype.

	Schizophrenia (N=172)		Bipolar disorder (N=116)	
COMT genotype	Met	Val/Val	Met	Val/Val
Caucasian				
Male	45	12	21	10
Female	29	12	50	14
African American				
Male	24	22	2	1
Female	5	10	4	6
Other races				
Male	5	4	3	2
Female	4	0	2	1
Smoking History				
Current smoker	61	32	26	14
Former smoker	27	13	17	5
Never smoker	24	15	39	15)
Number of cigarettes smoked per day†	19.9±11.9	16.0±10.6	16.2±13.7	16.5±11.0

† Never smokers were excluded to calculate the number of cigarettes smoked per day.
SCZ: Schizophrenia; BP: Bipolar Disorder

sex, age and race were significant factors for daily tobacco smoking within the group with schizophrenia (F (3, 129) =3.55, p=0.02). There was a trend showing that COMT Met carriers smoked more cigarettes daily than the Val/Val carriers (t (131) =1.84, p=0.07) in patients with schizophrenia since the Met carriers smoked 19.9±11.9 and the Val/Val carriers smoked 16.0±10.6 cigarettes/day, respectively. Among patients with bipolar disorder, there was no (t (60) =0.08, p=0.94) significant difference in the number of cigarettes smoker per day between the Met allele carriers and the Val/Val genotype. In addition, there were no significant differences between the COMT genotypes and smoking status among the current, former and never smokers in the whole group (χ^2=0.60, p value=0.74) and in the each diagnostic group evaluated separately.

Sex and genotype effects were also examined. In subjects with schizophrenia subdivided according to the COMT genotypes, there were significant differences in the number of cigarettes smoked per day (F (3, 129) =3.55, p=0.02; Figure 1). The Met female patients (N=25) smoked 24.4±13.9 cigarettes per day while the Val/Val male patients (N=32) smoked 14.7±10.0 cigarettes per day. Subjects who never smoked were excluded due to lack of contribution to the number of cigarettes smoked per day.

Racial and genotype effects were also determined among Caucasians and African Americans with schizophrenia and bipolar disorder. Other ethnical groups were excluded due to a small number of subjects in these diagnostic groups. In male and female patients with schizophrenia, the Met carriers smoked more than the Val/Val genotype carriers (t (59) =2.13, p=0.04, Figure 2) among African Americans. The Met carriers (N=29) smoked 14.0±8.2 cigarettes per day and the Val/Val carriers (N=32) smoked 9.7±7.4 cigarettes per day. Within African American female patients with schizophrenia, the Met carriers smoked more cigarettes daily than African American female patients with the Val/Val genotype (t (10) =3.46, p=0.006,

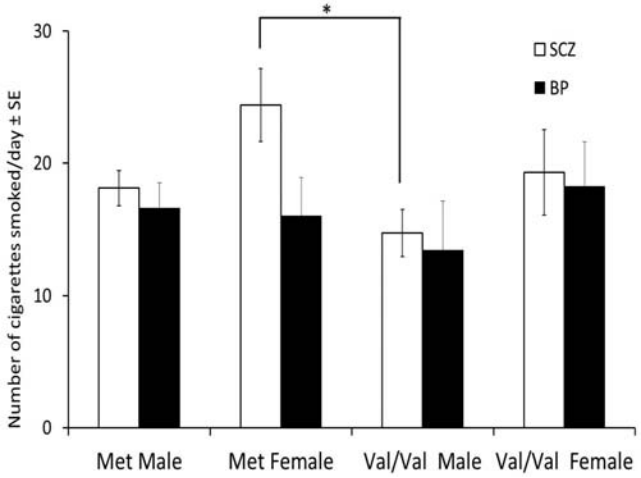

Figure 1: COMT Met females with schizophrenia smoked more cigarettes per day than the Val/Val males (p<0.01). SCZ: Schizophrenia; BP: Bipolar Disorder.

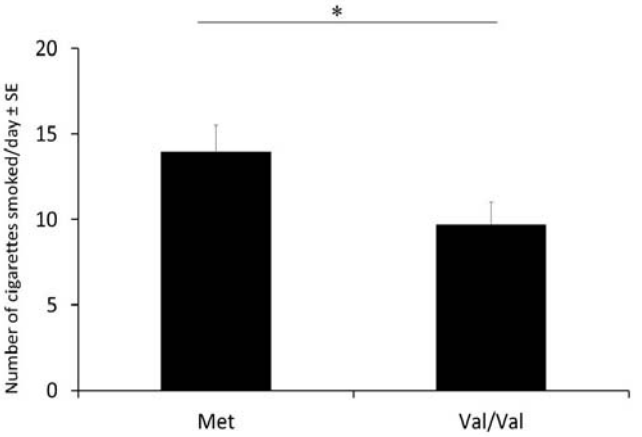

Figure 2: In African American with schizophrenia who had the COMT Met carriers smoked more than the Val/Val carriers (p=0.037).

Figure 3). The Met carriers (N=5) smoked 23.0±6.7 cigarettes per day, and the Val/Val carriers (N=10) smoked 9.05±8.5 cigarettes per day, respectively. No significant (t (73) =0.03, p=0.98) genotype effects on the number of cigarettes smoked per day were found in Caucasian patients with schizophrenia. There were no significant (F (2, 59) =.75, p=0.48) differences in the number of cigarettes smoked per day between the COMT genotype carriers among bipolar patients. Racial and genotype differences in life time smoking status were not found in both groups of mentally ill subjects.

Discussion

Overall, this study detected significant sex- and ethnic-related effects of the COMT genotypes on tobacco smoking only in smokers with schizophrenia. Specifically, female schizophrenic patient carriers of the Met allele smoked more cigarettes per day than male Val/Val genotype carriers. Racial differences were found, showing that all African Americans with schizophrenia, and female African Americans with schizophrenia, who carried the Met allele smoked more than the Val/Val genotype carriers. Regarding subjects with

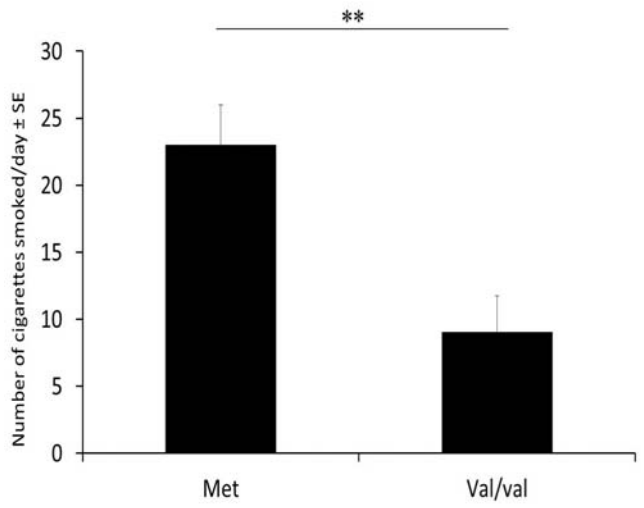

Figure 3: In African American females with schizophrenia who had the COMT Met carriers smoked more than the Val/Val allele carriers (p=0.006).

bipolar disorder, the COMT variants did not significantly affect smoking status or number of cigarettes smoked per day. This lack of association might be explained by the subject's current mood state that may contribute to the complex smoking behavior due to changes in DA neurotransmission [40]. Although all bipolar patients in the present study were currently euthymic, the relationship between bipolar disorder moods, cigarette smoking and the DA reward system deserves further study. For both diagnostic groups, possible effect of atypical and typical antipsychotic medication on smoking status was examined, and found a lack of effect of medication on daily tobacco consumption. The Val/Val genotype had greater DA release in response to smoking a cigarette in healthy control subjects [41]. Similarly, the Val/Val genotype carriers had greater satisfaction than the Met allele carriers with the same dose of nicotine applied via transdermal patch [42]. Based on these data, we hypothesized that patients with the Met allele would take more nicotine to satisfy their reinforcement by DA, induced by tobacco smoking. The present results showed that after controlling for the sex and ethnic group, African-American female Met allele carriers smoked more cigarettes per day than Val/Val allele carriers with schizophrenia.

Sex and COMT genotype differences have been reported in various psychiatric phenotypes [43] and smoking [13, 31,44]. Males have higher baseline COMT activity compared to females [27]. Since the Met allele results in deficient enzymatic activity, it would be expected that females with the Met allele have higher baseline brain DA levels. In terms of baseline DA levels, Grace reported that 'background' tonic DA levels are proposed to regulate the intensity of the phasic DA release caused by DA neuron firing [45]. Female Met allele carriers appear to have a small DA response to stimuli, like nicotine, resulting in greater tobacco consumption. Furthermore, it has been reported that the COMT Met variant is likely to have a greater smoking reinforcement under stress [46]. Based upon this finding, smokers with mental disorders may feel more stress compared to healthy control subjects, and to cope with stress they smoke more.

Genotype and racial effects in smoking were also determined. Although COMT genotype was not significantly associated with smoking in either male of female Caucasian patients with schizophrenia in a previous paper [12], the present results indicate that the COMT genotype, race and sex are significant factors for tobacco smoking in a mixed racial population of patients with schizophrenia. Previously it was reported that ethnic-specific COMT haplotypes are associated with nicotine dependence in healthy control smokers [29]. Although the present study does not include a haplotype analysis, the results demonstrated evidence that the COMT Met allele is associated with smoking behavior in African American patients. Race increases the risk of schizophrenia and therefore, African Americans were found 3-fold more likely than Caucasians to be diagnosed with schizophrenia [47].

The limitations of this study are 1) smoking data collection was done by subject self-reports instead of biological markers, 2) a lack of a healy control group, 3) a lack of assessment of the stress levels, 4) small number of subjects for analyses of racial and sex effects, especially in African American females and 5) residual symptoms were not taken into account to explain the differences between male and female. The evaluation of stress levels should be involved in future studies using standardized rating scales. Although this study had the required statistical power and sample size, when total sample was subdivided according to diagnosis, gender and race, it lacked the power as well as sample size.

Conclusion

The COMT Met allele is associated with greater daily tobacco consumption with specific sex (female), ethnic (African American) and diagnosis (schizophrenia) effects. The results indicate that tobacco smoking behavior is controlled by various endogenous and environmental factors which should be considered to reduce smoking prevalence in subjects with mental disorders.

Acknowledgment

The present study was supported in part by the Department of Pharmacology Psychopharmacology Research Fund C361024, Education and Research Development Fund 276157 for EFD and NIMH (R01 MH082784), NIH-NCCR, GCRC Program (UL1RR024986), the Chemistry Core of the Michigan Diabetes Research and Training Center (NIH5P60 DK 20572), (all Bethesda, Maryland) and the Washtenaw Community Health Organization (WCHO, Ann Arbor, Michigan), The Brain and Behavior Research Foundation (formerly NARSAD, Great Neck, New York), and the Prechter Longitudinal Study of Bipolar Disorder (Ann Arbor, Michigan) for VLE.

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J Schizophr Res - Volume 2 Issue 3 - 2015
ISSN : 2471-0148 | www.austinpublishinggroup.com

Citation: Hirasawa-Fujita M, Bly MJ, Ellingrod VL, Dalack GW, Pivac N and Domino EF. Association between COMT Val158Met and Tobacco Smoking among Subjects with Schizophrenia and Bipolar Disorder: A Pilot Study. J Schizophr Res. 2015; 2(3): 1017.