

Association Between the Catechol-O-Methyltransferase Val158Met Polymorphism and Cocaine Dependence

Falk W Lohoff^{*1}, Andrew E Weller¹, Paul J Bloch¹, Aleksandra H Nall¹, Thomas N Ferraro¹, Kyle M Kampman², Helen M Pettinati², David W Oslin², Charles A Dackis², Charles P O'Brien² and Wade H Berrettini¹

¹Department of Psychiatry, Translational Research Laboratories, Center for Neurobiology and Behavior, University of Pennsylvania School of Medicine, Philadelphia, PA, USA; ²Department of Psychiatry, Treatment Research Center, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Dopaminergic brain systems have been documented to have a major role in drug reward, thus making genes involved in these circuits plausible candidates for susceptibility to substance use disorders. The catechol-O-methyltransferase (COMT) is involved in the degradation of catecholamines and a functional polymorphism (Val158Met) has been suggested to influence enzyme activity. In this study we hypothesize that genetic variation in the COMT gene contributes to increased risk for cocaine dependence. Cocaine-dependent individuals ($n = 330$) and screened unaffected normal controls ($n = 255$) were genotyped for three SNPs in the COMT gene (rs737865, rs4680 (Val158Met), rs165599). All cases and controls were of African descent. Genotype and allele frequencies differed significantly for the Val158Met polymorphism between cases ($f(\text{Met}) = 35\%$) and controls ($f(\text{Met}) = 27\%$) ($p = 0.004$; corrected $p = 0.014$; OR 1.44; 95% CI 1.12–1.86). Haplotype analysis showed a significant association for a two-marker haplotype rs737865–Val158Met ($p = 0.005$). Results suggest that variation in COMT increases risk for cocaine dependence. The low enzyme activity 158Met allele or haplotypes containing this variant might have functional effects on dopamine-derived reward processes and cortical functions resulting in increased susceptibility for cocaine dependence. Additional studies are required to elucidate the role of COMT in the pathophysiology of substance use disorders.

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INTRODUCTION

Cocaine dependence is a devastating disorder with no FDA-approved pharmacological treatments available. Genetic studies estimate that 65–78% of the vulnerability risk for cocaine dependence is heritable (Kendler *et al*, 2000; Kendler and Prescott, 1998); however, identification of genetic risk factors remains difficult due to the complex mode of inheritance, clinical and genetic heterogeneity, and likely multiple genes involved, each contributing only a small effect to the overall risk. Dopaminergic brain systems have been documented to have a major role in drug reward (Dackis and O'Brien, 2005, 2001; Hyman *et al*, 2006), thus making genes involved in these circuits plausible candidates for susceptibility to substance use disorders (Lachman, 2006). The enzyme catechol-O-methyltransferase (COMT) is

involved in the degradation of catecholamines, including dopamine (Axelrod and Tomchick, 1958). The functional COMT polymorphism Val158Met affects enzyme activity, with the Val allele resulting in higher enzyme activity relative to the Met allele (Aksoy *et al*, 1993; Boudikova *et al*, 1990; Lachman *et al*, 1996; Lotta *et al*, 1995; Spielman and Weinshilbourn, 1981). Several studies suggest that the Val158Met polymorphism is involved in psychiatric phenotypes, including schizophrenia and bipolar disorder (Craddock *et al*, 2006; Tunbridge *et al*, 2006), and might further contribute to the comorbid substance abuse/dependence spectrum across psychiatric disorders. Although cocaine blocks the dopamine transporter primarily, leading to enhanced postsynaptic effects of dopamine signaling, COMT remains an important regulatory element in dopamine homeostasis. Emerging evidence suggests that COMT variation influences prefrontal cortex (PFC) dopamine regulation and might modulate aspects of cognition, emotions, and behavior (Egan *et al*, 2001; Tunbridge *et al*, 2006). PFC dysfunction might be an important component in cocaine dependence that contributes to loss of control and denial (Dackis and O'Brien, 2005). Individual differences in COMT activity might therefore influence vulner-

*Correspondence: FW Lohoff, Department of Psychiatry, Translational Research Laboratories, Center for Neurobiology and Behavior, University of Pennsylvania School of Medicine, 125 South 31st Street, Philadelphia, PA 19104, USA, Tel: +1 215 573 4582, Fax: +1 215 573 2041, E-mail: lohoff@mail.med.upenn.edu

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ability to cocaine dependence and other substance use disorders. In this study we tested the hypothesis that the functional Val158Met variation of the *COMT* gene increases susceptibility to cocaine dependence in individuals of African descent.

MATERIALS AND METHODS

DNA samples from cocaine-dependent individuals of African-American descent ($n=330$; 72% male subjects, mean age: 43) were collected during clinical studies of cocaine dependence at the University of Pennsylvania Treatment Research Center. Subjects were at least 18 years of age and were all assessed with the Structured Clinical Interview for DSM Disorders and urine drug screens were obtained. All patients had a clinical diagnosis of cocaine dependence as defined by *DSM-IV*. Family history was not obtained and ethnicity was determined by self-report. Exclusion criteria were all psychiatric axis I disorders except alcohol dependence/abuse and nicotine dependence. In addition to these exclusion criteria, participants were excluded if they had a history of a seizure disorder (except cocaine-induced seizures) or a severe medical illness, including a history of AIDS (but not merely of HIV + status). Individuals currently being treated with psychotropic medications or with psychiatric symptoms, including psychosis, dementia, suicidal or homicidal ideation, mania or depression requiring antidepressant therapy were excluded from these studies. Control samples from persons of African descent ($n=255$; 29% male subjects, mean age: 40) were collected at the University of Pennsylvania, Thomas Jefferson University and through the National Institute of Mental Health Genetics Initiative (www.nimhgenetics.org). Control individuals were screened for history of substance use disorders or other psychiatric illness. Control subjects were not assessed with a urine drug screen and ethnicity determination was by self-report. Subjects with a history of substance dependence or a history of major psychiatric illness (schizophrenia and unipolar or bipolar illnesses) as defined by *DSM-IV* criteria were excluded from this study (Berrettini and Persico, 1996). All protocols were approved by the Institutional Review Boards at Thomas Jefferson University and the University of Pennsylvania and all subjects provided written informed consent before DNA sample collection.

Genotyping of three SNPs across the *COMT* gene was performed using the Applied Biosystems Inc. (Foster City, CA, USA) 'Assays-on-demand' (ABI) SNP genotyping assay as per manufacturers protocol (SNP1: rs737865; SNP2: rs4680 (Val158Met); SNP3: rs165599). SNPs were selected based on findings in previous studies (Shifman *et al*, 2002), including studies of nicotine dependence in African-American subjects (Berrettini *et al*, 2007) (Figure 1). Genotyping quality control was assured by genotyping 10% duplicates for cases and controls. Concordance rate of genotypes was >99.5%.

Statistical Analyses

Genotypes and allele frequencies were compared between groups using χ^2 contingency analysis. A two-tailed type I error rate of 5% was chosen for the analysis. Linkage

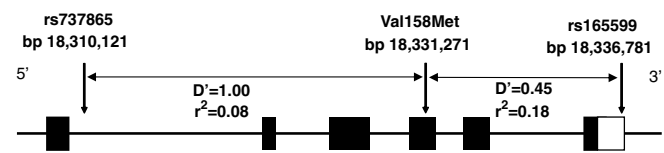


Figure 1 Diagram of the *COMT* gene and the three SNPs examined, with linkage disequilibrium D' values. Values in bp refer to chromosome 22, taken from the March 2006 assembly of the human genome sequence at www.genome.ucsc.edu. Exons are indicated by shaded boxes. The unshaded box represents the 3' UTR in exon 6. D' values represent African-American sample results.

disequilibrium (LD) and haplotype frequencies were estimated using the COCAPHASE program (Dudbridge, 2003). The COCAPHASE program uses standard unconditional logistic regression analysis. Correction for multiple testing was performed using permutation correction by the COCAPHASE program. This approach corrects for multiple testing but takes into account the correlation between markers. It is thus less conservative than a Bonferroni correction, which is appropriate for independent tests such as unlinked markers. For the single-marker analyses, 10 000 permutations were carried out to estimate the significance of the best results, correcting for the three loci tested. Haplotype analysis was performed using a two- and three-marker window. Rare haplotypes were excluded from analysis as the EM algorithm does not accurately estimate haplotype frequencies <1% (Fallin and Schork, 2000). The most significant p -value was corrected by permutation analysis as described above.

Our sample size had reasonable power to detect a disease association at a p -value less than or equal to 0.05, assuming an odds ratio of 1.5 and a minor allele frequency of 30% (99% for a log-additive mode of inheritance, 92% for a dominant, and 56% for a recessive mode of inheritance). Power analysis was performed using the Quanto program (Gauderman, 2002).

RESULTS

None of the genotype counts deviated significantly from those expected from Hardy-Weinberg equilibrium for cases or controls. Genotype and allele frequencies differed significantly for the Val158Met polymorphism between cocaine-dependent individuals ($f(\text{Met})=35\%$) and normal controls ($f(\text{Met})=27\%$) ($p=0.004$; corrected $p=0.014$; OR 1.44; 95% CI 1.12–1.86). SNP1 and SNP3 did not show a statistical difference between cases and controls (Table 1). There was no significant gender effect for any of the tested SNPs. Allele frequencies were consistent with those reported in the literature for individuals of African descent (Berrettini *et al*, 2007). Haplotype analysis showed significant associations for two-marker analysis and a trend for the three-marker combination (Table 2); however, after correction for multiple testing only the rs737865–rs4680 haplotype remained statistically significant. The patient group carried the major allele of rs737865 and the Met158 allele more often (33%) compared to controls (26%) ($p=0.005$; corrected $p=0.02$; OR 1.44). Haplotype analysis results appear to be driven by the Val158Met SNP,

Table 1 Genotype and Allele Frequencies of Variations in the *COMT* Gene

| SNP | Sample | n | Genotype frequency | | | p^a | Allele frequency | p^b |
|------------------------|----------|-----|--------------------|---------|---------|-------|------------------|--------------------|
| rs737865 | Cocaine | 330 | A/A | A/G | G/G | 0.312 | f(A) | 0.766 |
| | Controls | 253 | 0.715 | 0.255 | 0.030 | | 0.842 | |
| Val158Met ^c | Cocaine | 324 | Val/Val | Val/Met | Met/Met | 0.011 | f(Met) | 0.004 ^d |
| | Controls | 255 | 0.688 | 0.296 | 0.016 | | 0.836 | |
| rs165599 | Cocaine | 324 | A/A | A/G | G/G | 0.258 | f(A) | 0.196 |
| | Controls | 255 | 0.417 | 0.469 | 0.114 | | 0.349 | |
| | | | | | | | 0.271 | |
| | | | | | | | 0.674 | |
| | | | | | | | 0.710 | |

^aType I error rates for comparison of genotype frequencies between cocaine-dependent individuals and controls.

^bType I error rates for comparison of allele frequencies between cocaine-dependent individuals and controls.

^cVal158Met = rs4680 (Val = G).

^dGlobal significance after permutation correction for multiple testing: $p = 0.014$, standard error (SE) = 0.001175.

Table 2 Analysis of Common Haplotypes in the *COMT* Gene

| Haplotype | Case Frequency | Control Frequency | OR | χ^2 | p |
|--|----------------|-------------------|-------|----------|-------------------|
| <i>rs737865</i> – <i>rs4680</i> ^a | | | | | |
| A-Val | 325 | 0.520 | 289 | 0.580 | 1 3.962 0.046 |
| A-Met | 211 | 0.338 | 130 | 0.261 | 1.443 7.84 0.005 |
| G-Val | 88 | 0.141 | 79 | 0.158 | 0.990 0.675 0.411 |
| <i>rs4680</i> ^a – <i>rs165599</i> | | | | | |
| Val-A | 341.5 | 0.542 | 308.2 | 0.604 | 1 4.547 0.032 |
| Val-G | 73.51 | 0.116 | 63.77 | 0.125 | 1.04 0.277 0.598 |
| Met-A | 86.51 | 0.137 | 53.77 | 0.105 | 1.452 2.829 0.092 |
| Met-G | 128.5 | 0.204 | 84.23 | 0.165 | 1.377 3.282 0.070 |
| <i>rs737865</i> – <i>rs165599</i> | | | | | |
| A-A | 358.8 | 0.555 | 295.2 | 0.583 | 1 0.879 0.348 |
| A-G | 184.2 | 0.285 | 127.8 | 0.252 | 1.186 1.535 0.215 |
| G-A | 76.22 | 0.118 | 62.81 | 0.124 | 0.998 0.175 0.675 |
| G-G | 26.78 | 0.041 | 20.19 | 0.039 | 1.091 0.107 0.742 |
| <i>rs737865</i> – <i>rs4680</i> ^a – <i>rs165599</i> | | | | | |
| A-Val-A | 259.6 | 0.437 | 230.7 | 0.470 | 1 1.274 0.259 |
| A-Val-G | 59.42 | 0.10 | 57.27 | 0.116 | 0.922 0.929 0.335 |
| A-Met-A | 78.42 | 0.132 | 47.27 | 0.096 | 1.475 3.673 0.055 |
| A-Met-G | 120.6 | 0.203 | 81.73 | 0.166 | 1.311 2.566 0.109 |
| G-Val-A | 76 | 0.127 | 73 | 0.149 | 0.925 0.998 0.317 |

Best p -value 0.00511; global significance after permutation correction:

$p = 0.0263$, SE = 0.0016.

^ars4680 = Val158Met (Val = G) = rs4680.

supporting the hypothesis that the Val158Met polymorphism is a causative functional SNP.

DISCUSSION

In the present study, we show an association between the Val158Met polymorphism of the *COMT* gene and cocaine

dependence in individuals of African descent. Furthermore, we identify a risk haplotype contributing to the susceptibility for cocaine dependence. To our knowledge, this is the first report of an association of the *COMT* Val158Met polymorphism in cocaine dependence in individuals of African descent; however, given the high comorbidity of polysubstance abuse in individuals using cocaine, our result might reflect an association of a broader phenotype of substance use disorders. In fact, several previous studies have implicated the Val158Met polymorphism in a variety of substance abuse disorders (Table 3) (Beuten *et al*, 2005; Enoch *et al*, 2006; Horowitz *et al*, 2000; Hosak *et al*, 2006; Li *et al*, 2004; Samochowiec *et al*, 2006; Sery *et al*, 2006; Tiihonen *et al*, 1999; Vandenberg *et al*, 2000, 1997; Wang *et al*, 2001); however, others could not replicate results (Cevoli *et al*, 2006; Guo *et al*, 2007; Hallikainen *et al*, 2000; Kauhanen *et al*, 2000; Kweon *et al*, 2005) and there is no clear consensus on whether the Val allele or the Met allele increases risk (Table 3). This locus heterogeneity might indicate that the *COMT* Val158Met polymorphism is only one important variation in a cascade of regulatory systems, and depending on other genes or environmental factors, a higher or lower enzyme activity might predispose to substance use disorders. The *COMT* Val158Met polymorphism, rather than a single allele, might thus have an effect on pathways commonly shared between all substance use disorders. Such pathways include the reward system and cognitive functions influencing substance use behavior.

Dysregulation of *COMT*, which is the major enzyme involved in the degradation of dopamine in the frontal cortex (Karoum *et al*, 1994), might have primarily effects on cognitive processes involved in substance dependence and indirect downstream effects on the reward system, as suggested by recent neuroimaging data (Goldstein and Volkow, 2002; Volkow *et al*, 2002). Our results suggest an increased Met allele (low activity allele) frequency in cocaine users (35%) compared to normal controls (27%) ($p = 0.004$; corrected $p = 0.014$) in individuals of African descent. This finding is in line with the results of Hosak *et al* (2006) who showed higher novelty seeking scores in methamphetamine-dependent individuals with a Met allele (Hosak *et al*, 2006) and the observation that Met/Met

Table 3 Case–Control Association Studies of the COMT Val158Met Polymorphism in Substance Use Disorders

| Author | Year | Substance use disorder | Ethnicity | Sample size (n) | Val 158 frequency | Met 158 frequency | p-value allele frequency |
|--------------------------|------|------------------------------------|----------------------|-------------------------------|-------------------|-------------------|--------------------------|
| Ishiguro <i>et al</i> | 1999 | Alcohol dependence | Japanese | Cases (175) Controls (354) | 0.70 0.69 | 0.30 0.31 | NS |
| Tiihonen <i>et al</i> | 1999 | Alcohol dependence | Finnish | Cases (123) Controls (267) | 0.39 0.49 | 0.61 0.51 | $p < 0.05^a$ |
| Hallikainen <i>et al</i> | 2000 | Alcohol dependence | Finnish | Cases (62) Controls (267) | 0.52 0.49 | 0.48 0.51 | NS ^b |
| Kweon <i>et al</i> | 2005 | Alcohol dependence | Korean | Cases (97) Controls (94) | 0.74 0.70 | 0.25 0.29 | NS ^c |
| Samochowiec <i>et al</i> | 2006 | Alcohol dependence | Polish | Cases (100) Controls (196) | Not reported | Not reported | NS |
| Sery <i>et al</i> | 2006 | Alcohol dependence | Czech | Cases (339) Controls (400) | 0.52 0.49 | 0.48 0.51 | NS ^d |
| Horowitz <i>et al</i> | 2000 | Heroin dependence | Israeli ^e | Cases (101) Controls (126) | 0.25 0.29 | 0.74 0.70 | NS ^f |
| Li <i>et al</i> | 2004 | Methamphetamine abuse | Chinese | Cases (416) Controls (435) | 0.74 0.68 | 0.26 0.32 | $p = 0.02$ |
| Suzuki <i>et al</i> | 2006 | Methamphetamine abuse (psychosis) | Japanese | Cases (143) Controls (200) | 0.68 0.62 | 0.31 0.37 | NS |
| Guo <i>et al</i> | 2007 | Nicotine dependence | Chinese | Cases (203) Controls (102) | 0.78 0.72 | 0.21 0.27 | NS ^g |
| Vandenbergh <i>et al</i> | 1997 | Polysubstance abuse (lifetime use) | Caucasian | Cases (185) Controls (124) | 0.54 0.44 | 0.46 0.56 | $p = 0.02$ |

Abbreviation: NS, not significant.

^aThis study also compared the allele frequency of the cases to the general population ($n = 3140$). The difference in allele frequency was significant ($p < 0.05$).

^bThis study supplemented the 51 Tiihonen *et al* study. Although 51 Tiihonen *et al* used type 1 alcohol-dependent cases, this study used type 2 alcohol-dependent cases. The same control populations were used in both studies, including the general population ($n = 3140$). The results were not statistically significant with either control population.

^cWhen subdividing alcoholic cases by violent behavior, a significant allele frequency difference was observed between violent alcoholics and nonviolent alcoholics ($p = 0.012$) as well as controls and nonviolent alcoholics ($p = 0.04$).

^dWhen subdividing populations by sex, a significant allele frequency difference was observed between male alcoholics and male controls ($p < 0.007$).

^eIsraeli includes both Palestinian Arabs and Israeli Jews.

^fFamily-based haplotype relative risk design implemented with allelic frequency ($p = 0.03$).

^gThis study also genotyped former smokers ($n = 66$). No association was indicated.

carriers have decreased efficiency of PFC information processing in response amphetamine (Mattay *et al*, 2003). Individuals with the low-activity COMT allele may have longer-lasting and more effective dopamine release in the brain, in particular in the PFC affecting higher cortical functions involved in substance use behavior.

Although our study provides evidence for an association between the Val158Met polymorphism and cocaine dependence, it could be possible that other variations that are in LD with the Val158Met SNP might contribute to the observed association or that a haplotype confers risk rather than a single SNP. Consistent with this possibility are several studies that found haplotypes to be associated with disease rather than with a single polymorphism (Berrettini *et al*, 2007; Shifman *et al*, 2002). Recent reports show that COMT haplotypes code for differences in enzyme activity (Diatchenko *et al*, 2005) and haplotype-specific mRNA secondary structure has functional effects on COMT protein synthesis and enzyme activity (Nackley *et al*, 2006). Our

haplotype analysis indicates a risk haplotype for rs737865 and Val158Met ($p = 0.005$; corrected $p = 0.02$; OR 1.44). Interestingly, both markers (rs737865 and Val158Met) are in strong LD and incorporate the SNPs in the functional haplotypes described by Nackley *et al* (2006). Additional studies are necessary to elucidate potential functional haplotypic variations. Furthermore, it might be necessary to investigate this chromosomal region in more depth, given recent evidence of copy-number variations in this region (Wong *et al*, 2007) and the close proximity of COMT to other interesting candidate genes, like ARVCF, a member of the catenin family, which is involved in cell–cell communication.

Even though we report a positive association between the COMT gene and cocaine dependence, it is possible that our finding might be a false-positive result due to population stratification. Case–control association studies of subjects with self-reported ancestries are not immune to population stratification (Freedman *et al*, 2004). Undetected differences

in population structure can mimic the signal of association and lead to false-positive results or real effects that are missed (Pritchard and Donnelly, 2001). This is a particular concern for analyses of samples of African-American descent, as recent studies indicate larger genetic admixture than previously thought (Parra *et al*, 2001; Pfaff *et al*, 2001; Tian *et al*, 2006; Zhu *et al*, 2004). In fact, the Met allele is less frequent in individuals of African descent (Ameyaw *et al*, 2000; DeMille *et al*, 2002; McLeod *et al*, 1994), and haplotypes in *COMT* show marked differences across populations (Palmatier *et al*, 1999). Possible strategies to control for these stratification issues are the use of genomic controls (Bacanu *et al*, 2000; Devlin and Roeder, 1999) and/or the use of a family-based association design, a strategy that matches the genotype of an affected offspring with parental alleles not inherited by the offspring (Spielman and Ewens, 1996). In addition to these potential issues of genetic heterogeneity and population stratification, it is also important to consider limitations of clinical heterogeneity. All patients were diagnosed according to *DSM-IV* criteria; however, comorbid use of alcohol and nicotine might have differed between patients. Furthermore, the control subjects were assessed using semistructured interviews but did not undergo urine drug testing. Although drug testing is useful in establishing a diagnosis, it might not be useful for assessment of controls as it does not rule out past exposure or substance use. Unreported or minimized substance abuse in the control population is thus an important limitation that needs to be considered. Finally, spurious positive association findings remain a valid concern as recently shown in a statistical simulation study of the *COMT* gene (Sullivan, 2007). Thus, our results should be interpreted with caution and ultimately require careful replication and confirmation in an independent population of patients and controls.

In summary, we show that the Val158Met polymorphism in the *COMT* gene is associated with cocaine dependence. In addition we have identified a *COMT* risk haplotype for cocaine dependence. Our results require confirmation in other populations, and additional studies are required to elucidate the role of *COMT* in the pathophysiology of substance use disorders.

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CONFLICT OF INTEREST/DISCLOSURE

The authors FWL, AEW, PJB, AHN, TNF, KMK, DWO, HMP, CAD, CPO, and WHB reported no biomedical financial interests or potential conflicts of interest.

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