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Short communication

# A delta-opioid receptor genetic variant is associated with abstinence prior to and during cocaine dependence treatment

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ABSTRACT

*Introduction:* An intronic polymorphism in the delta-opioid receptor gene (*OPRD1*) was previously associated with cocaine dependence in African-Americans. However, it is not known if the polymorphism (rs678849) is associated with dependence-related phenotypes within the cocaine dependent population.
*Methods:* Cocaine and alcohol dependent subjects were randomized to either topiramate or placebo. Abstinence from cocaine use was confirmed by urine drug screens for benzoylecgonine three times per week. Cocaine withdrawal and craving were assessed at randomization using the Cocaine Selective Severity Assessment (CSSA) and Minnesota Cocaine Craving Scale (MCCS), respectively. Subjects were also interviewed using the Addiction Severity Index (ASI). Genotype at rs678849 was determined for 105 African-American subjects and compared to cocaine abstinence, as well as scores for CSSA, MCCS, and ASI.
*Results:* African-American patients with the C/T or T/T genotypes (n = 40) were more likely to be abstinent at the first urine drug screen and more likely to be abstinent for the week prior to randomization compared to patients with the C/C genotype (n = 65). Subjects carrying the T allele were also more likely to have abstinent weeks over the course of the trial compared to those with the C/C genotype (RR = 1.88, 95% CI = 1.59-2.22, p = 0.0035). No effects of rs678849 genotype on withdrawal, craving, or addiction severity were observed.
*Conclusions:* A polymorphism in *OPRD1* appears to be associated with both cocaine dependence and cocaine use during treatment in African-Americans. Follow-up studies to confirm the effect on cocaine use are warranted.



## 1. Introduction

Cocaine dependence affects millions of people worldwide and the underlying molecular mechanisms of the disorder are not completely understood. We previously reported an association analysis of six *OPRD1* variants in cocaine dependent individuals and healthy controls. A single intronic variant, rs678849, was associated with cocaine dependence in African-Americans but not European-Americans; the minor T allele was more common in controls than in cases (Crist et al., 2013a). Genotype at rs678849 has also been associated with other addiction phenotypes. The polymorphism predicts the efficacy of methadone and Suboxone in treating opioid dependence in African-Americans (Crist et al., 2013b). In an earlier study of European-Americans, haplotypes containing rs678849 were associated with opioid dependence (Zhang et al., 2008). Two other variants in *OPRD1* were also nominally associated with cocaine dependence in that population (Zhang et al., 2008).

Although rs678849 has been associated with cocaine dependence in African-Americans, the effect of the variant on addiction severity phenotypes has not been studied within a cocaine dependent population. To address this issue, we studied the effect of rs678849 genotype on cocaine abstinence as measured by urine drug screens in cocaine dependent African-Americans enrolled in a randomized trial of topiramate versus placebo.

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## 2. Materials and methods

### 2.1. Subjects

The methods of the topiramate study have been previously described (Kampman et al., 2013). Briefly, subjects were treatment-seeking men and women with comorbid cocaine and alcohol dependence and were recruited at the University of Pennsylvania Treatment Research Center. Diagnoses of cocaine and alcohol dependence were made using the Structured Clinical Interview for DSM IV (SCID-IV; First et al., 1996). Drinking was assessed by Timeline Followback (TLFB; Sobell and Sobell, 1995) and subjects were required to meet the following drinking criteria: 1) drinking within 30 days of enrollment, 2) reporting a minimum of 48 standard alcoholic drinks for women and 60 standard drinks for men in a consecutive 30-day period over the 90-day period prior to enrollment, and 3) reporting 2 or more days of 5 or more drinks in males and 4 or more drinks in females in this same pre-treatment period. Subjects meeting DSM-IV criteria for dependence on additional drugs except nicotine and cannabis were excluded. Psychiatric exclusion criteria included psychosis, dementia, and the use of other psychotropic medications. All subjects signed informed consent prior to participation in the trial, after an investigator explained to them the study procedures. The study was reviewed and approved by the Institutional Review Board (IRB) of the University of Pennsylvania.

### 2.2. Data collection

Subjects began psychosocial therapy for up to three weeks and were then screened for abstinence from both cocaine and alcohol three times during the week prior to randomization (week 1). Abstinence during this period was defined as three consecutive days of abstinence determined by TLFB self-report and confirmed by urine drug screens for benzoylecgonine using fluorescent polarization assays for cocaine and breathalyzer tests for alcohol. Samples containing equal to or greater than 300 ng/ml of benzoylecgonine were considered positive. Eligible subjects were randomized to either topiramate or placebo at the start of week 2 and continued pharmacological treatment for 13 weeks. Weekly individual cognitive-behavioral therapy (CBT) was also provided for both treatment groups. Cocaine abstinence was assessed three times per week during treatment as described above. Abstinent weeks were defined as weeks in which a patient was abstinent at all three assessments. Alcohol use during the trial was assessed by TLFB self-report.

The Addiction Severity Index (ASI; McLellan et al., 1992) was used to assess the severity of addiction-related problems at randomization and three other times during the trial. The Minnesota Cocaine Craving Scale (MCCS) was used to measure cocaine craving intensity (MCCS-I), cocaine craving frequency (MCCS-F) and cocaine craving duration (MCCS-D) at the start of treatment (Halikas et al., 1991). Cocaine withdrawal symptoms were also measured using the Cocaine Selective Severity Assessment (CSSA) at the start of treatment (Kampman et al., 1998).

### 2.3. Genotyping and statistical analysis

Genotyping of rs678849 was performed using a Taqman SNP Genotyping Assay as previously described (Crist et al., 2013a). Due to the small number of individuals with the T/T genotype (n = 3), the T/T and C/T genotype groups were combined and compared to patients with the C/C genotype. Chi-square tests were used to compare the percentages of male patients, the most frequent route of cocaine administration, cocaine positive baseline urine tests, abstinence from cocaine over the week prior to randomization, and the percentage of days spent drinking during the trial. The Kolmogorov-Smirnov test was used to determine if the data sets for the ASI components, MCCS, CSSA, age, abstinent weeks, years of alcohol use to intoxication, days of alcohol use to intoxication in the last 30 days, years of cocaine use, and days of cocaine use in the last 30 days were normally distributed (Massey, 1951). Age, years of cocaine use, years of alcohol use to intoxication, days of alcohol use to intoxication in the last 30 days, MCCS, ASI-medical, and ASI-alcohol were normally distributed and analyzed by student's *t*-tests. All other data were analyzed by Wilcoxon rank-sum tests. A generalized estimating equation (GEE) was used to determine the associations between rs678849 genotype and abstinence when binary cocaine abstinence data for weeks 1 through 14 were taken as repeated measures. The GEE also included the effects of time, age, sex, and treatment group. Results are reported as relative risks (RRs) with 95% confidence intervals. In all analyses, missing urine tests were counted as positive.

## 3. Results

Only African-Americans from the topiramate study were analyzed since the previous associations between rs678849 and cocaine dependence were observed in that ethnic group but not European-Americans. DNA samples were available for 105 African-American patients. The demographic information for patients carrying the T allele (C/T or T/T genotypes) and patients with the C/C genotype is provided in Table 1. The two genotypic groups did not have statistically significant differences in the percentage of male patients, age, days of alcohol use to intoxication in the last 30 days, years of alcohol use to intoxication, most frequent route of cocaine administration, days of cocaine use in the last 30 days, or years of cocaine use.

During the trial, patients received psychosocial therapy for up to three weeks and then cocaine use was assessed by three urine drug screens in the week before randomization. Patients carrying the T allele were significantly more likely to submit a cocaine negative urine (70.0%) for the first drug screen compared to patients with the C/C genotype (47.7%, $p = 0.026$). T allele carriers were also more likely than C/C patients to abstain from cocaine for the entire week proceeding treatment randomization (55.0% vs 24.6%, $p = 0.0017$) and had more abstinent weeks overall ($3.2 \pm 3.9$ vs $5.6 \pm 4.6$, $p = 0.0027$). A generalized estimating equation was used to determine the effect of rs678849 genotype on cocaine use when weekly abstinence data were taken as repeated measures. Patients carrying the T allele were more likely to have abstinent weeks than patients with the C/C genotype (RR = 1.88, 95% CI = 1.59-2.22, $p = 0.0035$) (Fig. 1). The effect of time was also significant; the percentage of patients with abstinent weeks decreased over the course of the trial ($p = 1.4 \times 10^{-5}$) (Fig. 1). No significant effects were observed for age, sex, or treatment group. There was also no effect of genotype on the percentage of days spent drinking during the trial.

Prior to randomization, patients were interviewed using the ASI, which encompasses seven different problem domains. No significant differences were found between the genotype groups for the composite scores in any of these domains (Table 1). Craving and withdrawal measurements were also measured by the MCCS and CSSA, respectively. No significant effect of rs678849 genotype was observed for either of these metrics (Table 1).

## 4. Discussion

Although rs678849 has been associated with a number of phenotypes, the underlying effects of the polymorphism are unknown. Intronic variants may affect gene expression by altering *cis* regulatory elements or they may be associated with alternative splicing.