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Single nucleotide polymorphism near *CREB1*, rs7591784, is associated with pretreatment methamphetamine use frequency and outcome of outpatient treatment for methamphetamine use disorder

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ABSTRACT

Although stimulant dependence is highly heritable, few studies have examined genetic influences on methamphetamine dependence. We performed a candidate gene study of 52 SNPs and pretreatment methamphetamine use frequency among 263 methamphetamine dependent Hispanic and Non-Hispanic White participants of several methamphetamine outpatient clinical trials in Los Angeles. One SNP, rs7591784 was significantly associated with pretreatment methamphetamine use frequency following Bonferroni correction ($p < 0.001$) in males but not females. We then examined rs7591784 and methamphetamine urine drug screen results during 12 weeks of outpatient treatment among males with treatment outcome data available ($N = 94$) and found rs7591784 was significantly associated with methamphetamine use during treatment controlling for pretreatment methamphetamine use. rs7591784 is near *CREB1* and in a linkage disequilibrium block with rs2952768, previously shown to influence *CREB1* expression. The CREB signaling pathway is involved in gene expression changes related to chronic use of multiple drugs of abuse including methamphetamine and these results suggest that variability in CREB signaling may influence pretreatment frequency of methamphetamine use as well as outcomes of outpatient treatment. Medications targeting the CREB pathway, including phosphodiesterase inhibitors, warrant investigation as pharmacotherapies for methamphetamine use disorders.

1. Introduction

Methamphetamine is a potent psychostimulant and complications of chronic use and abuse include addiction, psychosis, and depression, as well as increased risk of medical problems including HIV, impaired immune system functioning, cardiomyopathy, neurocognitive dysfunction, and Parkinson Disease (Curtin et al., 2015; Dean et al., 2013; Glasner-Edwards et al., 2010; Panenka et al., 2013; Salamanca et al., 2014; Won et al., 2013). Current treatment is limited to behavioral therapies and risk of relapse following behavioral treatment is high (Brecht and Herbeck, 2014; Lee and Rawson, 2008). Pharmacotherapy may improve outcomes with behavioral treatment but despite numerous clinical trials no effective medication is available for methamphetamine use disorder (Brensilver et al., 2013). Negative clinical trials to date have primarily tested medications approved for other indications and focused on medications targeting the monoamine neurotransmitter systems suggesting that the identification of new targets for medications is necessary for the successful development of effective medications for methamphetamine use disorder.

Substance use disorders are influenced by both biological and social factors although studies estimating heritability in excess of 50% for substance use disorders suggest an important role for genetic influences (Wetherill et al., 2015). For example, a recent study estimated heritability for stimulant use disorder at 68% (Ystrom et al., 2014). While numerous studies have examined the genetics of alcohol, nicotine, cannabis, opioid, and cocaine use disorders, relatively few studies have assessed the genetics of methamphetamine dependence (Demers et al., 2014; Jones and Comer, 2015; Palmer et al., 2015). A genome-wide association study (GWAS) of methamphetamine dependence in a sample from Asia found significant associations between a diagnosis of methamphetamine dependence and single nucleotide polymorphisms (SNPs) clustered

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in genes for cell adhesion molecules including *CDH13* and *CSMD1* (Uhl et al., 2008). A GWAS of amphetamine-response in healthy volunteers also identified SNPs in *CDH13* as the most significant SNPs associated with subjective response to amphetamine (Hart et al., 2012). In addition, a recent GWAS found several SNPs near *CREB1* were significantly associated with opioid response as well as lower risk of polydrug use in volunteers with methamphetamine dependence and altered *CREB1* expression (Nishizawa et al., 2014).

Studies examining genetic associations with phenotypes of relevance to treatment for substance use disorders may identify new targets for treatments for addiction. Higher pre-treatment methamphetamine use frequency is associated with greater severity of methamphetamine use disorder, worse clinical outcomes for outpatient treatment, and differential pharmacotherapy response (Heinzerling et al., 2014; Hillhouse et al., 2007; Ma et al., 2013). Urine drug screens detect recent drug use, are used ubiquitously as a treatment outcome measure in addiction treatment and clinical trials, and are associated with long term outcomes following outpatient treatment for stimulant use disorders (Carroll et al., 2014). We performed a candidate gene study of pre-treatment methamphetamine use frequency and urine drug screen results during treatment among methamphetamine dependent Hispanic and Non-Hispanic White participants of several outpatient methamphetamine dependence clinical trials in Los Angeles. We selected SNPs in *CDH13* given the two GWAS identifying variants in *CDH13* associated with methamphetamine dependence and subjective response to amphetamine (Hart et al., 2012; Uhl et al., 2008) as well as SNPs associated with opioid response in a recent GWAS (Nishizawa et al., 2014). Given the small number of methamphetamine genetic studies to date, we also included SNPs associated in previous studies with other phenotypes with relevance to methamphetamine dependence such as dependence on nicotine, cocaine, or alcohol, functioning of dopaminergic systems, brain structure, and other psychiatric diseases. A detailed rationale for each SNP is provided in Table S1.

2. Methods

2.1. Participants and study design

Data for the current study were taken from several methamphetamine dependence outpatient clinical trials at UCLA. Each trial had a similar design and inclusion/exclusion criteria and recruited volunteers seeking treatment for methamphetamine problems via print, radio, and internet ads. Participants visited a UCLA outpatient research clinic and completed the informed consent process, including separate consent for genotyping. Participants then underwent a battery of clinical assessments including the Structured Clinical Interview for DSM-IV (SCID), assessment of substance use, including the self-reported number of days with methamphetamine, marijuana, alcohol, and tobacco use during the past 30 days prior to entering the trial, and collection of blood for genotyping. Those participants meeting trial eligibility criteria then underwent outpatient treatment, including weekly cognitive behavioral therapy sessions and study medication (active or placebo assigned randomly) for 8–12 weeks. During treatment, participants visited the clinic thrice weekly for urine drug screens for methamphetamine.

Participants included in the current analysis (N = 263) met the following criteria: (1) aged 18 and older, (2) seeking treatment for methamphetamine problems, (3) methamphetamine dependent per DSM-IV-TR criteria as assessed by the SCID, (4) completed baseline substance use frequency assessments, (5) provided consent and blood for genotyping, and (6) Hispanic or Non-Hispanic White ancestry based on results of genotyping a panel of ancestry-informative markers (details below). Demographics of the sample included in the current analysis are shown in Table S2. The study was approved by the UCLA IRB and the clinical trials from which data is obtained were each registered with clinicaltrials.gov (NCT00469508, NCT01011829, NCT01365819, NCT00833443).

2.2. SNP selection and genotyping

Sixty four (64) candidate SNPs hypothesized to be associated with methamphetamine use frequency were selected for genotyping (Table S1). SNPs were selected on the basis of previous research associating the SNP with methamphetamine dependence or a related phenotype such as response to amphetamine in healthy volunteers, other psychiatric conditions such as ADHD, depression, schizophrenia, dependence on other substances such as cocaine, alcohol, or nicotine, dopaminergic functioning, and functional or structural brain imaging phenotypes. When available, preference was given to SNPs identified in previous GWAS studies over those from previous candidate gene studies. One candidate SNP of interest, rs2952768, which was associated with opioid sensitivity and severity of methamphetamine dependence in a Japanese GWAS (Nishizawa et al., 2014) was not able to be genotyped on the genotyping platform used and was replaced by two nearby SNPs also associated with opioid sensitivity in the GWAS: rs7591784 and rs2709386. Details of the SNPs and the rationale for their selection is provided in Supplemental Table S1. In addition, a panel of 128 ancestry-informative markers (AIMs) were genotyped in order to assess for and control population stratification by ancestry (Kosoy et al., 2009).

Whole blood (10 cc) was collected from participants via venipuncture and DNA was extracted via Gentra Autopure LS nucleic acid purification instrument and then frozen and stored at −20 °C for genotyping later. SNPs were genotyped using Fluidigm SNP Type™ assays with the Fluidigm Biomark™ HD system (South San Francisco, CA) at the UCLA genotyping core facility. SNPtype™ assays and reagents for each of the SNPs were purchased from Fluidigm. Genotype calls were made using the Fluidigm SNP Genotying Analysis Software and genotype cluster plots for each SNP were examined manually for quality control. Of the 64 candidate SNPs, 6 SNPs failed genotyping quality control (single allele called with single cluster on manual inspection of genotype plot) and were removed, leaving 58 candidate SNPs genotyped and available for analysis. Two of the AIM SNPs also failed genotyping leaving 126 AIMs for analysis. Of the 58 SNPs genotyped, 6 SNPs were in very high LD ($D' \approx 1$) with other genotyped SNPs and were eliminated from further analyses leaving 52 SNPs for the candidate gene association analysis. After initial quality control, seventeen genotype values were missing and were imputed by sampling the missing genotype from the empirical distribution over all other individuals' genotype at that SNP.

2.3. Data analysis

Ancestry was evaluated using the 126 genotyped AIMs. A reference population was obtained from the HGDP-CEPH Human Genome Diversity Cell Line Panel (http://www.hagsc.org/hgdp/), containing genotype information for over 1043 individuals. Using only the 126 AIMs common to both the reference data and the present study, the Bayesian clustering algorithms implemented in STRUCTURE v2.3 (Falush et al., 2003; Pritchard et al., 2000) were used to estimate population admixture proportions. In order to determine the optimal number of ancestry-specific clusters, the log-likelihood of the data was evaluated as a function of cluster size. The choice to use a total of four separate clusters was made since the increase in the log-likelihood after adding the fifth group was