Title

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

Authors

Heinzerling, Keith G
Demirdjian, Levon
Wu, Yingnian
et al.

Publication Date

2016-03-01

DOI

10.1016/j.jpsychires.2015.12.008

Peer reviewed

HHS Public Access

Author manuscript

J Psychiatr Res. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

J Psychiatr Res. 2016 March ; 74: 22–29. doi:10.1016/j.jpsychires.2015.12.008.

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

Keith G. Heinzerling[a,*], **Levon Demirdjian**[b], **Yingnian Wu**[b], and **Steven Shoptaw**[a]

[a] UCLA Department of Family Medicine and Center for Behavioral and Addiction Medicine, Los Angeles, CA, USA

[b] UCLA Department of Statistics, Los Angeles, CA, USA

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.

[*] Correspondence to: Keith Heinzerling, UCLA Department of Family Medicine, 1920 Colorado Avenue, Santa Monica, CA, 90404, USA, kheinzerling@mednet.ucla.edu.

Conflicts of Interest

Drs. Heinzerling and Shoptaw have received previous research funding from MediciNova, Cephalon, Pfizer, and Philip Morris. Dr. Heinzerling has received research funding from Alkermes and has been an advisor to Gilead. The authors declare no conflicts of interest resulting from this funding and the current study.

Contributors

Dr. Heinzerling was responsible for the study concept and design. Drs. Heinzerling and Shoptaw were responsible for data collection. Mr. Demirdjian and Dr.Wu analyzed the data. Drs. Heinzerling and Wu and Mr. Demirdjian interpreted the results. Dr. Heinzerling drafted the manuscript and all authors provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

Keywords

methamphetamine; pharmacotherapy; genetics; *CREB1*; sex; ancestry

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 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 to 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 two nearby SNP 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 ge notyped 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' ≈ 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 individual' 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 1,043 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 minimal. Moreover, no individual had predominant ancestry from the fifth group when a total of five groups were used. After setting the number of distinct ancestry-specific groups to four, ancestry of the individuals in the current study was determined using the reference population over 25 runs in STRUCTURE. A total of 20,000 burn-ins and 50,000 iterations were performed in each run. CLUMPP v1.1 software (Jakobsson and Rosenberg, 2007) was then used to adjust for permutations between the 25 runs and to align all four population clusters. The ancestry corresponding to each cluster was determined by aligning the ancestries in the reference

group to the individuals in the current study. The proportion of ancestry from each of the four clusters was then calculated for each individual. A total of 265 Hispanic White (European cluster >= 0.15 and Native American cluster >= 0.25) and Non-Hispanic White (European cluster >= 0.50 and Native American cluster <= 0.25) participants were included in the candidate gene analyses.

Initial analyses showed that sex and proportion of Native American Ancestry determined by AIMs were significantly associated with pretreatment methamphetamine use frequency and therefore methamphetamine use frequency analyses were performed stratifying by sex and controlling for proportion of Native American Ancestry. Separate linear regression models were run for each of the SNPs predicting pretreatment methamphetamine use frequency, controlling for age, proportion Native American ancestry and study, in men and women assuming an additive, dominant, and recessive genetic model. A Bonferroni corrected $p < 0.001$ was used as the threshold for statistical significance accounting for the 52 SNPs included in the analyses. None of the SNPs deviated significantly ($p < 0.001$) from expected Hardy-Weinberg equilibrium among Hispanic or Non-Hispanic Whites. A linkage disequilibrium (LD) plot for the region surrounding the most significant SNPs, rs7591784 and rs2709386, was created using HaploView, version 4.2 and genotype data from HapMap population CEU.

The SNP with the strongest association with pretreatment methamphetamine use frequency, rs7591784, was then assessed for association with methamphetamine urine drug screen results during outpatient treatment. This analysis was limited to male participants with treatment outcome data available (N = 94) from two clinical trials with identical 12 week outpatient treatment periods (Heinzerling et al., 2014, Heinzerling et al., 2010). Generalized estimating equations using a first order auto-regressive correlation structure were fit to longitudinal data for methamphetamine urine drug screen results collected 3 times a week over a 12 week outpatient treatment period. Separate models were run for the additive, recessive, and dominant genetic models, controlling for pretreatment methamphetamine use, study, smoking status, and proportion Native American ancestry. The method of multiple imputations (Enders 2010, McPherson et al. 2013) was used to deal with missing treatment outcomes, where logistic regression was used to impute intermittent missing values. A total of 50 imputed datasets were created and the results were combined using Rubin's rules (Rubin 1987).

3. Results

3.1. Pretreatment methamphetamine use frequency

Male sex ($\beta = -5.58$, SE = 1.24, $t = -4.49$, $p = 1.09 \times 10^{-5}$) and increasing proportion of Native American ancestry assessed via ancestry informative markers ($\beta = -7.18$, SE = 2.76, $t = -2.61$, $p = 0.0097$) were both significantly associated with lower frequency of methamphetamine use after controlling for age, study, and tobacco, alcohol, and marijuana use (N = 263). As a result, subsequent models for each SNP were run with the sample stratified by sex and controlling for proportion Native American ancestry.

Assuming an additive genetic model, three of the 52 SNPs investigated were nominally associated ($p < 0.05$) with pretreatment methamphetamine use frequency in males after controlling for age, proportion Native American ancestry and study (Table 1): rs7591784 ($p = 0.00029$) and rs2709386 ($p = 0.0076$), both located on chromosome 2 in the intergeneic region near *CREB1* and *METTL21A* (Figure 1), and rs11640875 (p = 0.0242) in *CDH13*. Only rs7591784 remained significant after Bonferroni correction ($p < 0.001$, Figure 2) and none of these three SNPs were significant in females assuming an additive model (Table 1). Only rs163030 in *WDR41* was nominally significant in females assuming an additive genetic model (p = 0.0167) but did not survive Bonferroni correction. Several other SNPs were nominally significant assuming a recessive genetic model but did not meet the Bonferroni corrected threshold for significance including rs6265 in *BDNF* (p = 0.0215), rs12922394 in *CDH13* (p = 0.0243), and rs12576775 in *TENM4* (p = 0.0246) in males and rs588765 in CHRNA5 (p = 0.0063) and rs192599 in *CDH13* (p = 0.0356) in females (Table S3). Assuming a dominant genetic model, rs7591784 and rs2709386 near *CREB1* and rs11640875 in *CDH13* were nominally significant in males but not females (Table S4).

3.2. Methamphetamine treatment outcomes

The SNP most strongly associated with pretreatment methamphetamine use frequency, rs7591784, was then tested for association with methamphetamine use during treatment controlling for pretreatment methamphetamine use. As rs7591784 was associated with pretreatment methamphetamine use among males only, this analysis was limited to males. Among male participants with treatment outcome data available (N = 94), rs7591784 was significantly associated with the probability of testing positive for methamphetamine via urine drug screens during a 12 week treatment period assuming a dominant genetic model and controlling for pretreatment past 30 day methamphetamine use frequency, study, cigarette smoker status, and proportion Native American ancestry. Participants homozygous for the minor G allele were significantly less likely to provide urine specimens positive for methamphetamine during treatment (OR = 0.175, S.E. = 0.274, $\bar{p} = 9.1 \times 10^{-5}$, S.E.($\bar{p}$) = 0.0002, where $\bar{p}$ is the average p-value over 50 imputed datasets) compared to participants with at least one A allele (AG/AA, Figure 3). Results using an additive or a recessive genetic model and without imputation of missing data yielded similar results, although with a larger *p* value, and the addition of covariates for active versus placebo conditions from the clinical trials did not change the results (data not shown).

4. Discussion

We performed a candidate gene study of methamphetamine treatment among methamphetamine dependent Hispanic and Non-Hispanic Whites participating in several methamphetamine clinical trials and found one SNP, rs7591784, was significantly associated with methamphetamine use both before and during outpatient treatment in males but not females. Higher pretreatment methamphetamine use frequency is a marker of greater severity of methamphetamine use disorder and is a strong predictor of continued methamphetamine use and poor treatment outcomes during outpatient treatment for methamphetamine use disorder (Heinzerling et al., 2014, Hillhouse et al., 2007). The identification of an association between rs7591784 and pretreatment methamphetamine use

frequency provides insight into the biological mechanisms influencing severity of methamphetamine use disorders and may also identify targets for new treatments for the group with the highest pretreatment use frequency, who respond poorly to existing behavioral therapies. Given the strong association between higher pretreatment methamphetamine use frequency and poor treatment outcomes, it is not surprising that rs7591784 was associated both with pretreatment frequency of methamphetamine use and methamphetamine use assessed via urine drug screens during subsequent outpatient treatment. But the association between rs7591784 and methamphetamine urine drug screen results during treatment was strongly significant after controlling for pretreatment methamphetamine use frequency suggesting that rs7591784 is associated with treatment outcomes independent of pretreatment use frequency.

SNP rs7591784 is on chromosome 2 in the intergeneic region near *CREB1* and *METTL21A* (Figure 4). CREB is a transcription factor that mediates changes in gene expression resulting from chronic exposure to a variety of drugs of abuse including methamphetamine and has been shown to influence drug reward, self-administration, and relapse in multiple animal models of addiction (Larson et al., 2011, Nestler, 2013). Methamphetamine increases phosphorylated CREB, the active form of the transcription factor, via striatal dopamine receptor-mediated activation of adenylate cyclase resulting in increased cAMP and activation of protein kinase A (Cadet et al., 2015). Phosphorylated-CREB then binds to the promoters of genes implicated in methamphetamine-induced epigenetic changes and neuroplasticity that are thought to underlie the persistent risk of relapse characteristic of addiction, such as *c-fos*, *fosB*, and *BDNF*, increasing expression of these genes in the striatum (Krasnova et al., 2013). CREB also mediates methamphetamine-induced astrocyte activation and increased expression of sigma-1 receptors (Zhang et al., 2015) which may contribute to neuroinflammatory changes observed in methamphetamine addiction (Ray et al., 2014). A SNP in *CREB1*, rs10932201, was associated with sensitivity to reward and activation of brain regions important in addiction including the nucleus accumbens during a reward-related decision making task among healthy young adults (Wolf et al., 2015). A GWAS of opioid response in a Japanese sample found that the C allele of rs2952768, which is in an LD block with rs7591784 (D’ = 97; Figure 4), was significantly associated with greater postoperative opioid analgesic requirements, as well as lower reward dependence in healthy volunteers, lower risk of polydrug use in volunteers with methamphetamine dependence, alcohol dependence, and eating disorders, and increased expression of *CREB1* in human postmortem brains (Nishizawa et al., 2014). The G (minor) allele in rs7591784 was associated in our study with lower pretreatment methamphetamine use and better treatment outcomes, both suggestive of less severe methamphetamine use disorder, and as rs7591784 and rs2952768 are strongly linked, our results provide support for the previous association between the C (minor) allele of rs2952768 and lower severity of methamphetamine use disorder observed in the Japanese GWAS. Whether rs7591784 directly effects CREB expression or function is not known, but our results and previous studies suggest that variability in CREB signaling and subsequent changes in methamphetamine-induced gene expression may influence clinical severity of methamphetamine use problems and success in quitting methamphetamine and that the CREB signaling pathway may be a target for the development of medications to treat

methamphetamine use disorder. Phosphodiesterase inhibitors modulate signaling via the CREB pathway via increases in cAMP and ibudilast, a nonselective phosphodiesterase inhibitor, is in clinical development for methamphetamine use disorder (NCT01860807).

Previous GWAS found SNPs in *CDH13* to be among the most significant SNPs associated with a diagnosis of methamphetamine dependence (Uhl et al., 2008) and with the subjective response to amphetamine among healthy volunteers (Hart et al., 2012). None of the SNPs related to *CDH13* in our study were significantly associated with methamphetamine use frequency following Bonferroni correction. The lack of significant association in our study may be due to the different phenotypes examined in the previous GWAS compared to the current study that examined methamphetamine use frequency in a treatment-seeking sample or may be due to limited power to detect SNPs with small effect size in our small sample.

Methamphetamine use frequency as well as results of our SNP analyses differed greatly between males and females. None of the three SNPs that were nominally significant in males, including rs7591784, approached significance in females ($p > 0.60$) suggesting that although the female sample size was relatively small, the lack of significant associations for these SNPs in females is unlikely to be due to limited power in females alone. Previous studies in rodents have found sex differences in methamphetamine pharmacokinetics (Milesi-Halle et al., 2015, Rambousek et al., 2014), methamphetamine-induced plasma corticosterone levels (Zuloaga et al., 2014), methamphetamine-related neurotoxicity (Bourque et al., 2011), and methamphetamine self-administration with female rats acquiring methamphetamine self-administration faster, self-administering more methamphetamine, and exhibiting higher rates of methamphetamine reinstatement than male rats (Roth and Carroll, 2004, Ruda-Kucerova et al., 2015). In humans, female methamphetamine users have a higher risk of Parkinson's disease (Curtin et al., 2015), greater reductions in hippocampal volume (Du et al., 2015) and higher prevalence of physiologic dependence symptoms (Wu et al., 2009) compared to male methamphetamine users and these biological or other psycho-social differences may have a greater influence on methamphetamine use frequency in females than the SNPs examined here. Interestingly, amphetamine-induced CREB-mediated transcription differs dramatically between male and female mice in the nucleus accumbens, ventral tegmental area, amygdala, and locus coeruleus with greater CREB-meditated gene transcription following amphetamine in females (Shaw-Lutchman et al., 2003) suggesting that the significant association between rs7591784 and methamphetamine-related phenotypes observed in our study in males but not females may be due to underlying sexual dimorphism in the CREB signaling pathway. The one SNP that was nominally associated with methamphetamine use frequency assuming an additive model in females, rs163030, was associated with caudate volume in a GWAS (Stein et al., 2011) and rs163030 may influence methamphetamine use frequency in females by altering structure or functioning of the caudate, a brain region implicated in impulsivity and methamphetamine addiction (Lee et al., 2009). Additional studies investigating sex differences in the biological and social influences on methamphetamine addiction are warranted.

This study has several limitations. The sample size is small and the power to detect an association between a candidate SNP and methamphetamine use frequency with a small effect size is limited. As a result the study is subject to false negative results. Also, numerous

findings from candidate gene studies have failed to replicate (Hart et al., 2013) and results from this study are preliminary and require replication in an independent sample prior to making any conclusions. To mitigate this risk, we emphasized selection of candidate SNPs that had previously been associated with methamphetamine-relevant phenotypes in GWAS. Our study did not genotype rs2709386, which was most strongly associated with opioid sensitivity in the previous Japanese GWAS, and although rs2709386 and rs7591784 are highly linked, future studies are necessary to determine which SNP is more strongly associated with methamphetamine use and treatment outcomes. Lastly, the sample was drawn participants of several methamphetamine pharmacotherapy clinical trials and results from a treatment-seeking sample may not be generalizable to methamphetamine uses as a whole.

In summary, we found an association between rs7591784 near *CREB1* and pretreatment methamphetamine use, an important indicator of disease severity and predictor of subsequent treatment outcomes, as well as methamphetamine use during treatment independent of pretreatment methamphetamine use in males but not females. Replication of this result in independent samples is necessary but our results combined with previous research suggest that variability in CREB signaling may influence severity of methamphetamine use disorder as well as success in quitting methamphetamine with outpatient treatment and that medications targeting the CREB pathway such as the non-selective phosphodiesterase inhibitor ibudilast may be effective treatments for methamphetamine use disorder. Future studies should examine the role of CREB-related polymorphisms and the associated epigenetic changes on response to treatment for methamphetamine use disorder and whether these biological influences on methamphetamine use differ between males and females.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The study was funded by NIH grant K23 DA023558 to Dr. Heinzerling. Mr. Demirdjian was supported by a Burroughs Wellcome Fund Population and Laboratory Based Sciences Award at UCLA. Genotyping was performed by the UCLA Genotyping and Sequencing Core which is supported by NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR000124.

Role of the Funding Source

The funders had no role in the study design, the collection, analysis and interpretation of data, the writing of the report, or the decision to submit the article for publication.

References

Bourque M, Liu B, Dluzen DE, Di Paolo T. Sex differences in methamphetamine toxicity in mice: effect on brain dopamine signaling pathways. Psychoneuroendocrinology. 2011; 36(7):955–69. [PubMed: 21236583]

Brecht ML, Herbeck D. Time to relapse following treatment for methamphetamine use: a long-term perspective on patterns and predictors. Drug Alcohol Depend. 2014; 139:18–25. [PubMed: 24685563]

Brensilver M, Heinzerling KG, Shoptaw S. Pharmacotherapy of amphetamine-type stimulant dependence: an update. Drug Alcohol Rev. 2013; 32(5):449–60. [PubMed: 23617468]

Cadet JL, Brannock C, Jayanthi S, Krasnova IN. Transcriptional and epigenetic substrates of methamphetamine addiction and withdrawal: evidence from a long-access self-administration model in the rat. Molecular neurobiology. 2015; 51(2):696–717. [PubMed: 24939695]

Carroll KM, Kiluk BD, Nich C, Devito EE, Decker S, Lapaglia D, et al. Toward empirical identification of a clinically meaningful indicator of treatment outcome: Features of candidate indicators and evaluation of sensitivity to treatment effects and relationship to one year follow up cocaine use outcomes. Drug Alcohol Depend. 2014; 137c:3–19.

Curtin K, Fleckenstein AE, Robison RJ, Crookston MJ, Smith KR, Hanson GR. Methamphetamine/amphetamine abuse and risk of Parkinson's disease in Utah: a population-based assessment. Drug Alcohol Depend. 2015; 146:30–8. [PubMed: 25479916]

Dean AC, Groman SM, Morales AM, London ED. An evaluation of the evidence that methamphetamine abuse causes cognitive decline in humans. Neuropsychopharmacology. 2013; 38(2):259–74. [PubMed: 22948978]

Demers CH, Bogdan R, Agrawal A. The Genetics, Neurogenetics and Pharmacogenetics of Addiction. Current behavioral neuroscience reports. 2014; 1(1):33–44. [PubMed: 25045619]

Du J, Quan M, Zhuang W, Zhong N, Jiang H, Kennedy DN, et al. Hippocampal volume reduction in female but not male recent abstinent methamphetamine users. Behavioural brain research. 2015; 289:78–83. [PubMed: 25920682]

Falush D, Stephens M, Pritchard JK. Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. Genetics. 2003; 164(4):1567–87. [PubMed: 12930761]

Glasner-Edwards S, Mooney LJ, Marinelli-Casey P, Hillhouse M, Ang A, Rawson RA. Psychopathology in methamphetamine-dependent adults 3 years after treatment. Drug Alcohol Rev. 2010; 29(1):12–20. [PubMed: 20078677]

Hart AB, de Wit H, Palmer AA. Candidate gene studies of a promising intermediate phenotype: failure to replicate. Neuropsychopharmacology. 2013; 38(5):802–16. [PubMed: 23303064]

Hart AB, Engelhardt BE, Wardle MC, Sokoloff G, Stephens M, de Wit H, et al. Genome-wide association study of d-amphetamine response in healthy volunteers identifies putative associations, including cadherin 13 (CDH13). PloS one. 2012; 7(8):e42646. [PubMed: 22952603]

Heinzerling KG, Swanson AN, Hall TM, Yi Y, Wu Y, Shoptaw SJ. Randomized, placebo-controlled trial of bupropion in methamphetamine-dependent participants with less than daily methamphetamine use. Addiction. 2014; 109(11):1878–86. [PubMed: 24894963]

Heinzerling KG, Swanson AN, Kim S, Cederblom L, Moe A, Ling W, et al. Randomized, double-blind, placebo-controlled trial of modafinil for the treatment of methamphetamine dependence. Drug Alcohol Depend. 2010; 109(1-3):20–9. [PubMed: 20092966]

Hillhouse MP, Marinelli-Casey P, Gonzales R, Ang A, Rawson RA. Predicting in-treatment performance and post-treatment outcomes in methamphetamine users. Addiction 102 Suppl. 2007; 1:84–95.

Jakobsson M, Rosenberg NA. CLUMPP: a cluster matching and permutation program for dealing with label switching and multimodality in analysis of population structure. Bioinformatics (Oxford, England). 2007; 23(14):1801–6.

Jones JD, Comer SD. A review of pharmacogenetic studies of substance-related disorders. Drug Alcohol Depend. 2015

Kosoy R, Nassir R, Tian C, White PA, Butler LM, Silva G, et al. Ancestry informative marker sets for determining continental origin and admixture proportions in common populations in America. Human mutation. 2009; 30(1):69–78. [PubMed: 18683858]

Krasnova IN, Chiflikyan M, Justinova Z, McCoy MT, Ladenheim B, Jayanthi S, et al. CREB phosphorylation regulates striatal transcriptional responses in the self-administration model of methamphetamine addiction in the rat. Neurobiology of disease. 2013; 58:132–43. [PubMed: 23726845]

Larson EB, Graham DL, Arzaga RR, Buzin N, Webb J, Green TA, et al. Overexpression of CREB in the nucleus accumbens shell increases cocaine reinforcement in self-administering rats. J Neurosci. 2011; 31(45):16447–57. [PubMed: 22072694]

Lee B, London ED, Poldrack RA, Farahi J, Nacca A, Monterosso JR, et al. Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. J Neurosci. 2009; 29(47):14734–40. [PubMed: 19940168]

Lee NK, Rawson RA. A systematic review of cognitive and behavioural therapies for methamphetamine dependence. Drug Alcohol Rev. 2008; 27(3):309–17. [PubMed: 18368613]

Ma JZ, Johnson BA, Yu E, Weiss D, McSherry F, Saadvandi J, et al. Fine-grain analysis of the treatment effect of topiramate on methamphetamine addiction with latent variable analysis. Drug Alcohol Depend. 2013; 130(1-3):45–51. [PubMed: 23142494]

Milesi-Halle A, Hambuchen MD, McMillan DE, Michael Owens S. The pharmacokinetics of methamphetamine self-administration in male and female rats. Drug Alcohol Depend. 2015; 150:164–9. [PubMed: 25796510]

Nestler EJ. Cellular basis of memory for addiction. Dialogues in clinical neuroscience. 2013; 15(4): 431–43. [PubMed: 24459410]

Nishizawa D, Fukuda K, Kasai S, Hasegawa J, Aoki Y, Nishi A, et al. Genome-wide association study identifies a potent locus associated with human opioid sensitivity. Mol Psychiatry. 2014; 19(1):55–62. [PubMed: 23183491]

Palmer RH, Brick L, Nugent NR, Bidwell LC, McGeary JE, Knopik VS, et al. Examining the role of common genetic variants on alcohol, tobacco, cannabis and illicit drug dependence: genetics of vulnerability to drug dependence. Addiction. 2015; 110(3):530–7. [PubMed: 25424661]

Panenka WJ, Procyshyn RM, Lecomte T, MacEwan GW, Flynn SW, Honer WG, et al. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. Drug Alcohol Depend. 2013; 129(3):167–79. [PubMed: 23273775]

Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. Genetics. 2000; 155(2):945–59. [PubMed: 10835412]

Rambousek L, Kacer P, Syslova K, Bumba J, Bubenikova-Valesova V, Slamberova R. Sex differences in methamphetamine pharmacokinetics in adult rats and its transfer to pups through the placental membrane and breast milk. Drug Alcohol Depend. 2014; 139:138–44. [PubMed: 24726427]

Ray LA, Roche DJ, Heinzerling K, Shoptaw S. Opportunities for the development of neuroimmune therapies in addiction. International review of neurobiology. 2014; 118:381–401. [PubMed: 25175870]

Roth ME, Carroll ME. Sex differences in the acquisition of IV methamphetamine self-administration and subsequent maintenance under a progressive ratio schedule in rats. Psychopharmacology (Berl). 2004; 172(4):443–9. [PubMed: 14654996]

Ruda-Kucerova J, Amchova P, Babinska Z, Dusek L, Micale V, Sulcova A. Sex Differences in the Reinstatement of Methamphetamine Seeking after Forced Abstinence in Sprague-Dawley Rats. Frontiers in psychiatry. 2015; 6:91. [PubMed: 26217239]

Salamanca SA, Sorrentino EE, Nosanchuk JD, Martinez LR. Impact of methamphetamine on infection and immunity. Frontiers in neuroscience. 2014; 8:445. [PubMed: 25628526]

Shaw-Lutchman TZ, Impey S, Storm D, Nestler EJ. Regulation of CRE-mediated transcription in mouse brain by amphetamine. Synapse (New York, NY). 2003; 48(1):10–7.

Stein JL, Hibar DP, Madsen SK, Khamis M, McMahon KL, de Zubicaray GI, et al. Discovery and replication of dopamine-related gene effects on caudate volume in young and elderly populations (N=1198) using genome-wide search. Mol Psychiatry. 2011; 16(9):927–37. 881. [PubMed: 21502949]

Uhl GR, Drgon T, Liu QR, Johnson C, Walther D, Komiyama T, et al. Genome-wide association for methamphetamine dependence: convergent results from 2 samples. Arch Gen Psychiatry. 2008; 65(3):345–55. [PubMed: 18316681]

Wetherill L, Agrawal A, Kapoor M, Bertelsen S, Bierut LJ, Brooks A, et al. Association of substance dependence phenotypes in the COGA sample. Addiction biology. 2015; 20(3):617–27. [PubMed: 24832863]

Wolf C, Mohr H, Diekhof EK, Vieker H, Goya-Maldonado R, Trost S, et al. CREB1 Genotype Modulates Adaptive Reward-Based Decisions in Humans. Cerebral cortex (New York, NY : 1991). 2015

Won S, Hong RA, Shohet RV, Seto TB, Parikh NI. Methamphetamine-associated cardiomyopathy. Clinical cardiology. 2013; 36(12):737–42. [PubMed: 24037954]

Wu LT, Blazer DG, Patkar AA, Stitzer ML, Wakim PG, Brooner RK. Heterogeneity of stimulant dependence: a national drug abuse treatment clinical trials network study. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2009; 18(3): 206–18.

Ystrom E, Reichborn-Kjennerud T, Neale MC, Kendler KS. Genetic and environmental risk factors for illicit substance use and use disorders: Joint analysis of self and co-twin ratings. Behavior genetics. 2014; 44(1):1–13. [PubMed: 24196977]

Zhang Y, Lv X, Bai Y, Zhu X, Wu X, Chao J, et al. Involvement of sigma-1 receptor in astrocyte activation induced by methamphetamine via up-regulation of its own expression. Journal of neuroinflammation. 2015; 12(1):29. [PubMed: 25889537]

Zuloaga DG, Johnson LA, Agam M, Raber J. Sex differences in activation of the hypothalamic-pituitary-adrenal axis by methamphetamine. Journal of neurochemistry. 2014; 129(3):495–508. [PubMed: 24400874]

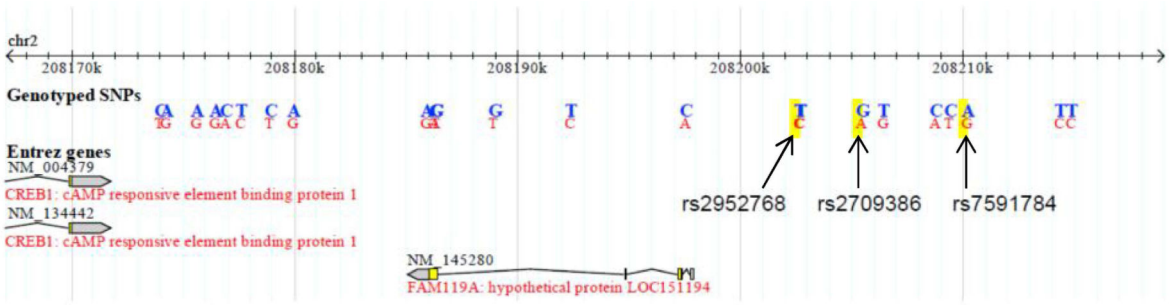

Figure 1.

Location of rs7591784 and rs2709386 associated with methamphetamine use frequency in current sample and rs2952768 associated with opioid response and *CREB1* expression in Nishizawa, Fukuda et al. 2014. SNPs are located on Chromosome 2 in an intergenic region near *FAM119A* (*METTL21A*) and *CREB1*.

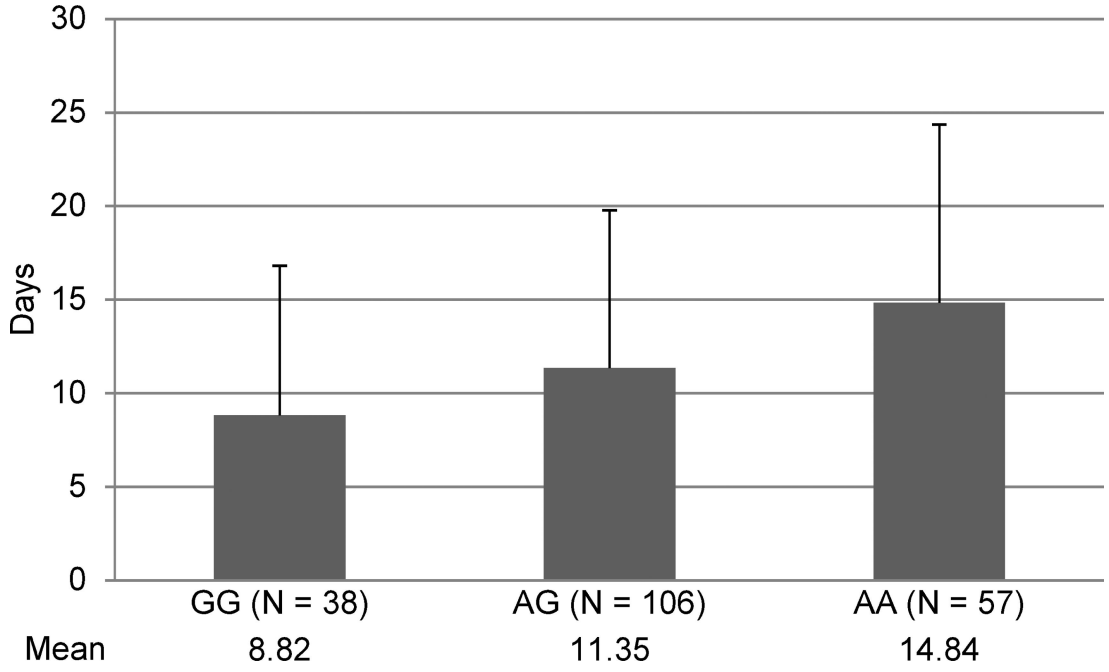

Figure 2.

Mean days in past 30 with methamphetamine use by rs7591784 genotype in methamphetamine dependent males. Error bars represent standard deviation of the mean.

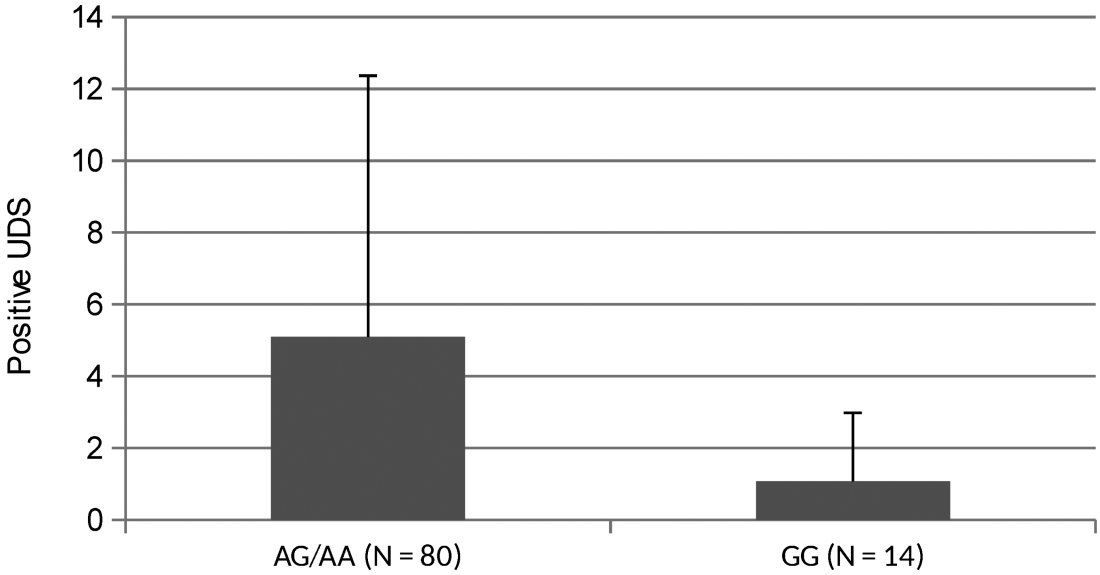

Figure 3.

Mean number of methamphetamine positive urine drug screens (UDS) by rs7591784 genotype. Error bars represent standard deviation of the mean.

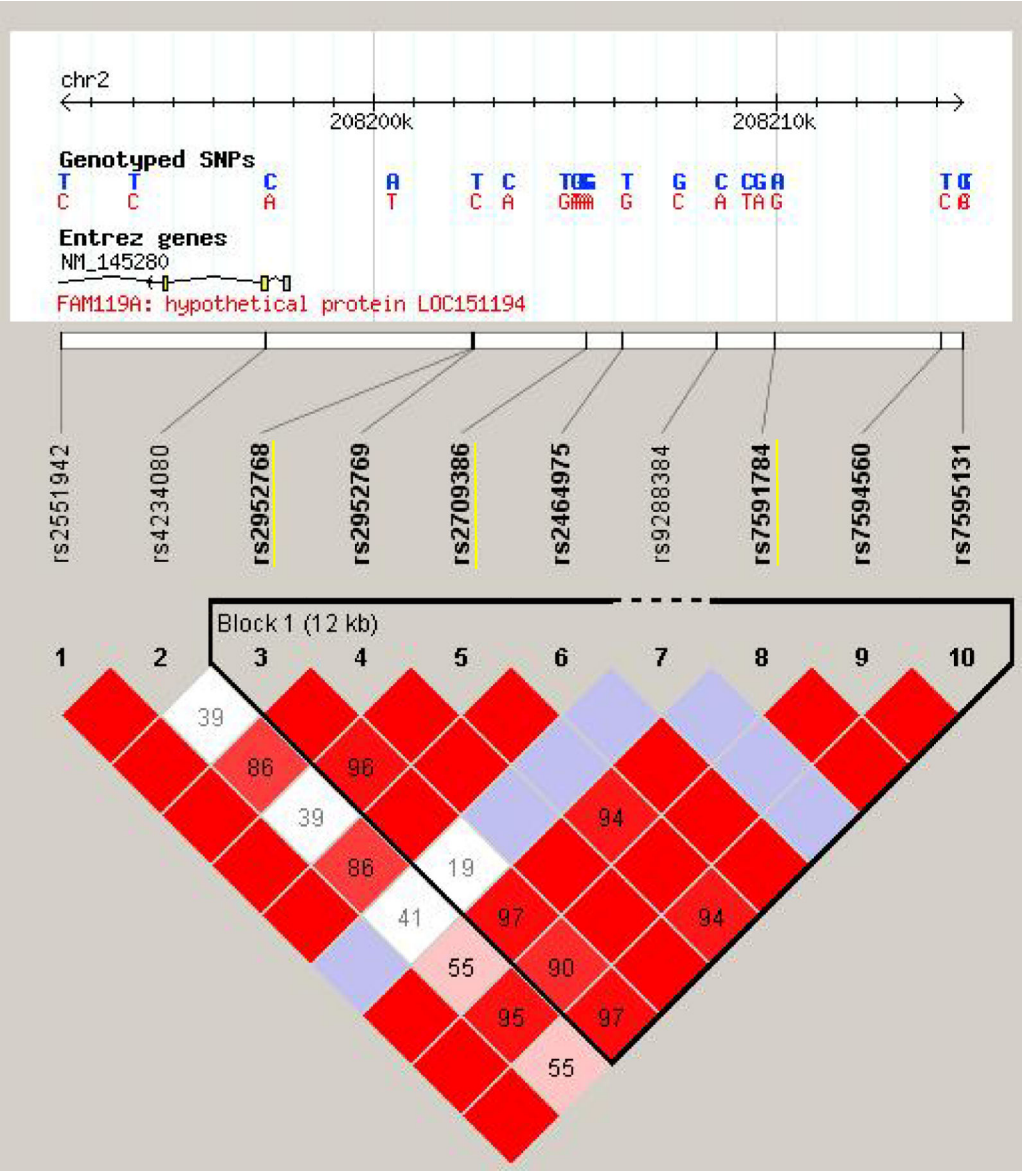

Figure 4.

LD plot showing linkage between rs7591784 and rs2709386 associated with methamphetamine use frequency in current sample and rs2952768 associated with opioid response and CREB1 expression in Nishizawa, Fukuda et al. 2014. Numbers in square = D' and color represents D'/LOD. Plot was created using HaploView, version 4.2 and genotype data from HapMap population CEU.

Table 1

Association between candidate SNPs and methamphetamine use frequency among methamphetamine dependent males and females assuming an additive genetic model

					Males					Females				
SNP	**Chr**	**Position**	**Gene**	**Alleles**	**MAF**	**Estimate**	**SE**	**t value**	***p* value**	**MAF**	**Estimate**	**SE**	**t value**	***p* value**
rs7591784	**2**	**207637006**	**near *METTL21A/CREB1***	**G/A**	**0.45**	**3.10**	**0.84**	**3.69**	**0.00029**	**0.40**	**−0.34**	**1.62**	**−0.21**	**0.8326**
rs2709386	**2**	**207632310**	**near *METTL21A/CREB1***	**A/G**	**0.39**	**−2.33**	**0.86**	**−2.70**	**0.0076**	**0.41**	**0.86**	**1.62**	**0.53**	**0.5981**
rs11640875	**16**	**82687819**	***CDH13***	**A/G**	**0.48**	**−1.97**	**0.87**	**−2.27**	**0.0242**	**0.44**	**0.04**	**1.60**	**0.02**	**0.9822**
rs12576775	11	79366149	*TENM4*	G/A	0.14	1.93	1.15	1.68	0.0956	0.07	−3.08	2.86	−1.08	0.2863
rs2535629	3	52799203	*ITIH3*	T/C	0.45	1.31	0.86	1.53	0.1281	0.42	1.40	2.00	0.70	0.4862
rs10503253	8	4323322	*CSMD1*	A/C	0.15	−1.71	1.19	−1.44	0.1503	0.13	1.68	2.39	0.70	0.4854
rs6265	11	27658369	*BDNF*	T/C	0.19	−1.58	1.11	−1.43	0.1550	0.15	0.13	2.41	0.06	0.9564
rs11150556	16	83236936	*CDH13*	T/C	0.42	−1.25	0.90	−1.39	0.1656	0.34	0.57	1.72	0.33	0.7442
rs588765	15	78573083	*CHRNA5*	T/C	0.31	1.14	0.87	1.31	0.1925	0.30	2.59	1.75	1.48	0.1449
rs11646213	16	82609046	upstream *CDH13*	A/T	0.46	−1.11	0.85	−1.30	0.1946	0.48	0.10	1.64	0.06	0.9532
rs13273442	8	42688874	near *CHRNB3*	A/G	0.27	−1.23	0.96	−1.29	0.1996	0.23	3.05	2.07	1.47	0.1462
rs26907	5	81069496	*RASGRF2*	T/C	0.21	−1.29	1.05	−1.22	0.2231	0.22	−1.02	1.81	−0.56	0.5756
rs11819869	11	46539130	*AMBRA1*	T/C	0.14	1.42	1.18	1.21	0.2282	0.15	−2.64	2.44	−1.08	0.2832
rs8045006	16	83222668	*CDH13*	A/C	0.07	−1.95	1.70	−1.15	0.2527	0.03	4.02	4.86	0.83	0.4122
rs16969968	15	78590583	*CHRNA5*	A/G	0.24	−1.05	0.99	−1.06	0.2895	0.22	−1.25	2.21	−0.57	0.5746
rs10514585	16	83250733	*CDH13*	T/C	0.26	0.98	0.95	1.02	0.3070	0.29	−0.10	1.93	−0.05	0.9590
rs237915	3	8768625	*OXTR*	C/T	0.27	0.94	1.03	0.91	0.3639	0.26	−1.20	2.07	−0.58	0.5661
rs1076560	11	113412966	*DRD2*	A/C	0.28	0.91	1.00	0.91	0.3657	0.23	−0.83	2.15	−0.39	0.6995
rs1800497	11	113400106	*ANKK1*	T/C	0.33	0.85	0.94	0.91	0.3668	0.27	1.13	2.20	0.52	0.6088
rs153227	5	81072493	*RASGRF2*	C/T	0.25	−0.90	1.01	−0.89	0.3729	0.26	−1.02	1.73	−0.59	0.5600
rs26908	5	81069982	*RASGRF2*	G/A	0.32	−0.77	0.87	−0.88	0.3788	0.29	−1.32	1.63	−0.81	0.4203
rs11646411	16	82713332	*CDH13*	G/C	0.09	1.21	1.42	0.86	0.3934	0.09	0.38	2.81	0.14	0.8922
rs8058532	16	83676061	*CDH13*	T/C	0.38	0.70	0.83	0.84	0.4027	0.45	0.53	1.77	0.30	0.7647
rs12922394	16	82638722	*CDH13*	T/C	0.11	−1.13	1.39	−0.81	0.4173	0.09	−1.02	3.36	−0.30	0.7627
rs153226	5	81075096	*RASGRF2*	G/A	0.40	−0.67	0.85	−0.79	0.4323	0.36	−1.68	1.50	−1.12	0.2669

					Males					Females				
SNP	**Chr**	**Position**	**Gene**	**Alleles**	**MAF**	**Estimate**	**SE**	**t value**	***p* value**	**MAF**	**Estimate**	**SE**	**t value**	***p* value**
rs684513	15	78566058	*CHRNA5*	G/C	0.36	−0.62	0.85	−0.73	0.4668	0.41	−1.49	1.82	−0.82	0.4158
rs9817063	3	114128261	*DRD3*	C/T	0.45	−0.61	0.86	−0.71	0.4792	0.45	−1.42	1.65	−0.86	0.3941
rs3865188	16	82617112	near *CDH13*	T/A	0.39	0.58	0.91	0.64	0.5249	0.34	−2.08	1.69	−1.23	0.2232
rs7206473	16	82867271	*CDH13*	G/C	0.43	−0.39	0.84	−0.47	0.6425	0.39	−2.32	1.55	−1.50	0.1386
rs8057927	16	82659207	*CDH13*	C/T	0.09	0.72	1.57	0.46	0.6449	0.12	−0.67	2.49	−0.27	0.7885
rs192599	16	82852633	*CDH13*	G/T	0.30	−0.35	0.90	−0.39	0.7004	0.26	−2.97	1.68	−1.77	0.0830
rs6277	11	113412737	*DRD2*	T/C	0.39	0.34	0.90	0.38	0.7083	0.45	0.66	1.81	0.37	0.7146
rs163030	**5**	**77485646**	***WDR41***	**A/C**	**0.39**	**0.33**	**0.92**	**0.36**	**0.7170**	**0.34**	**3.68**	**1.49**	**2.47**	**0.0167**
rs10514542	16	82524079	near *CDH13*	C/G	0.19	0.35	1.07	0.33	0.7404	0.19	−0.62	2.04	−0.30	0.7631
rs11191454	10	102900247	*AS3MT*	G/A	0.13	0.38	1.27	0.30	0.7662	0.18	2.45	2.19	1.12	0.2677
rs2799573	10	18312999	*CACNB2*	G/A	0.27	0.21	0.95	0.22	0.8266	0.23	−1.73	1.94	−0.89	0.3767
rs4680	22	19963748	*COMT*	A/G	0.44	0.14	0.92	0.16	0.8770	0.50	−1.35	1.84	−0.74	0.4641
rs3784943	16	83678830	*CDH13*	G/A	0.17	−0.15	1.00	−0.15	0.8820	0.17	0.00	2.32	0.00	0.9999
rs10514203	5	81077660	*RASGRF2*	A/G	0.07	−0.24	1.67	−0.14	0.8853	0.07	−2.71	3.36	−0.81	0.4234
rs7195409	16	83493987	*CDH13*	G/A	0.29	−0.13	0.95	−0.14	0.8877	0.21	−1.62	1.94	−0.84	0.4059
rs190409	5	81075502	*RASGRF2*	T/C	0.50	0.11	0.83	0.14	0.8916	0.47	0.77	1.50	0.51	0.6109
rs1024582	12	2293080	*CACNA1C*	T/C	0.27	0.13	0.95	0.13	0.8935	0.30	1.46	1.82	0.80	0.4252
rs1799971	6	154039662	*OPRM1*	G/A	0.16	0.14	1.10	0.13	0.8967	0.16	3.18	2.20	1.44	0.1548
rs6565113	16	83074041	*CDH13*	G/T	0.47	−0.11	0.85	−0.13	0.8970	0.48	−0.55	1.61	−0.34	0.7346
rs12051272	16	82629683	*CDH13*	T/G	0.02	0.31	2.80	0.11	0.9114	0.02	−3.16	5.64	−0.56	0.5774
rs5326	5	175443193	*DRD1*	A/G	0.15	−0.13	1.15	−0.11	0.9123	0.12	−3.73	2.85	−1.31	0.1954
rs12364283	11	113476233	*DRD2*	G/A	0.04	−0.20	2.26	−0.09	0.9300	0.08	−4.62	3.23	−1.43	0.1587
rs252587	5	81071815	*RASGRF2*	T/C	0.37	0.05	0.87	0.06	0.9523	0.35	1.53	1.59	0.96	0.3390
rs2910704	5	37827123	*GDNF*	C/G	0.40	0.05	0.92	0.06	0.9527	0.30	0.02	2.02	0.01	0.9922
rs26906	5	81069068	*RASGRF2*	A/G	0.15	−0.06	1.17	−0.06	0.9565	0.12	1.41	2.41	0.58	0.5621
rs578776	15	78596058	*CHRNA3*	T/C	0.47	0.03	0.85	0.04	0.9698	0.50	2.70	1.89	1.43	0.1577
rs7186123	16	82788147	*CDH13*	C/A	0.11	0.02	1.36	0.02	0.9855	0.10	2.08	2.95	0.71	0.4820

Notes: bold = p < 0.05 in males or females, SNP = reference SNP ID, Chr = chromosome, Position = chromosome position from GenBank human genome assembly 38, Alleles = minor/major, MAF = minor allele frequency, SE = standard error, rs11646213 minor allele is T in females, rs6277 minor allele is C in females.

J Psychiatr Res. Author manuscript; available in PMC 2017 March 01.