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Association study of the β-arrestin 2 gene (ARRB2) with opioid and cocaine dependence in a European American population

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Abstract

The rewarding properties of drugs of abuse are mediated by the Mu-Opioid Receptor (MOR). Genetic variation in MOR and MOR interacting proteins (MORIPs) involved in MOR signaling may increase risk for drug dependence. The MORIP, *B*-arrestin, plays an important role in the regulation of MOR trafficking thereby highlighting it as a candidate gene for addiction phenotypes. In this case-control association study, DNA samples from cocaine (n=336) and opioid-dependent (n=335) patients and controls (n=656) were genotyped for 7 single nucleotide polymorphisms (SNPs) (rs11868227, rs3786047, rs4522461, rs1045280, rs2271167, rs2036657, and rs4790694) across *ARRB2*, the gene encoding the *B*-arrestin 2 protein. No significant differences were observed in genotype or allele frequency between drug dependent and control individuals for any of the SNPs analyzed. Haplotype analysis was similarly negative. Further studies are needed to determine whether variation in *ARRB2* (or other MORIPs) are relevant to cocaine or opioid dependence in different ethnic populations or if they confer risk that is specific to dependence on other drugs of abuse.

Keywords

case-control association study; cocaine dependence; opioid dependence; *AARB2*

Introduction

Drug addiction is a major public health concern. Twin and family studies suggest that a large percentage of risk for opioid dependence (Merikangas et al., 1998; Tsuang et al., 1998; Karkowski et al., 2000; Kendler et al., 2003) and cocaine dependence (Zhang et al., 2006) (Kendler and Prescott, 1998; Karkowski et al., 2000; Kendler et al., 2000) is influenced by genetic factors (reviewed in (Kreek et al., 2005; Saxon et al., 2005; Yuferov et al., 2010). Variations in genes involved in the mechanisms of drug action have the potential to influence addiction risk and treatment outcomes. The opioid receptor system, and specifically *mu-opioid receptor* (MOR), has been studied extensively for its role in opioid dependence (Matthes et al., 1996; Sora et al., 1997). In addition, considerable evidence has

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shown that opioid receptors play a central role in the rewarding effects of various pharmacological classes of abused drugs via the disinhibition of ventral tegmental area (VTA) dopaminergic neurons. For example, MOR has been shown to be involved in mediating the rewarding effects of cocaine (Becker et al., 2002; Hall et al., 2004; Hummel et al., 2006).

Although several studies have analyzed the influence of single nucleotide polymorphisms (SNPs) in the gene encoding MOR (*OPRM1*) on risk for drug dependence, results are equivocal (Hoehe et al., 2000; Szeto et al., 2001; Crowley et al., 2003; Tan et al., 2003; Bart et al., 2004; Smith et al., 2005; Zhang et al., 2006). Since MOR interacts directly with multiple proteins called *MOR interacting proteins (MORIPs)*, MORIP gene polymorphisms may affect susceptibility to drug dependence. Of particular interest are the variations that occur within the gene encoding *β*-arrestin 2 (*ARRB2*), a known MORIP (Milligan, 2005).

β-arrestins, including β-arrestin 1 and β-arrestin 2, are expressed at high levels in the central nervous system (CNS) and play a critical role in the regulation of G-protein coupled receptors (GPCRs) including MOR. Compared to *β*arrestin-1, *β*arrestin-2 is involved in the mediation of agonist-dependent internalization and is faster at promoting GPCR recycling (reviewed in (Gainetdinov et al., 2004)). Specifically, *β*-arrestin 2 has been found to be an important regulator of signal transduction mediated by opioid receptors through promotion of receptor desensitization and internalization (Bohn et al., 2003; Gainetdinov et al., 2004; Haberstock-Debic et al., 2005). It also plays a role in opioid reward, tolerance, and analgesia (Bohn et al., 1999; Bohn et al., 2000; Bohn et al., 2002; Bohn et al., 2003).

In *ARRB2* null mutant animals, MOR does not undergo densensitization following chronic morphine and mice show increased and prolonged antinociceptive effects following morphine challenge (Bohn et al., 1999; Bohn et al., 2002). In a subsequent study, Bohn *et al.* explored the effects of abolishing MOR desensitization on the reinforcing and psychomotor properties of morphine and cocaine, reporting that *β*-arrestin-2 may mediate morphine-induced dopaminergic neurotrotransmission more so than cocaine (Bohn et al., 2003).

In a genome wide scan for genetic linkage to opioid dependence, a signal was detected near *ARRB2* thus highlighting this gene as a positional as well as biologically plausible candidate (Gelernter et al., 2006). The aim of this study was to evaluate the association between SNPs across the *ARRB2* gene and opioid and cocaine-dependence.

Materials and Methods

Sample collection

All protocols were approved by the Institutional Review Boards at the University of Pennsylvania. DNA samples from European American control individuals (n=656; male 50.8%) were collected from the National Institute of Mental Health Genetics Initiative (NIMH-GI) (www.nimhgenetics.org). Control individuals were screened for history of substance use disorders and other psychiatric illness. DNA samples from opioid-dependent (n=335; male 63.3%) and cocaine-dependent patients of European American decent (n=336; male 50.3%) meeting DSM-IV criteria for dependence were requested and acquired through the NIDA Center for Genetic Studies in conjunction with Washington University and Rutgers University Cell & DNA Repository. Opioid-dependent samples were acquired from the NIDA Repository Studies 1 (PI: J. Gelernter et al.), 5 (PI: M.J.Kreek), and 17 (PI: W.Berrettini) and cocaine-dependent samples were acquired from Studies 7 (PI: L. Bierut) and 13 (PI: J. Cubells). DNA samples were transferred to 96-well stock plates and diluted to a concentration of 1 ng/μl for genotyping.

SNP selection and genotyping

The *ARRB2* gene is located on chromosome 17:4,613,789-4,624,794 (Build 37/UCSC hg19/Feb.2009)(Supplemental Digital Content: Figure 1). Six SNPs (rs11868227 (intron), rs3786047 (intron), rs4522461(intron), rs1045280 (synonymous, exon 11), rs2271167 (intron), rs2036657(3'UTR) were genotyped across ARRB2. These SNPs were selected based on high heterozygosity and uniform coverage of the gene. rs11868227 was excluded from all further analysis because of a severe deviation from HWE in controls (p=0.007). The remaining 4 SNPs (rs2036657 was not genotyped in the HapMap Project CEU population (HapMap Data Rel 27 Phase II+III,Feb 09) covered 100% of the *ARRB2* gene (r^2=0.8) calculated using the Tagger algorithm implemented in Haploview software with a minor allele frequency (MAF) cut-off set at .20 (http://www.broadinstitute.org/haploview) (Barrett et al., 2005)(Supplemental Digital Content: Figure 2). rs4790694, located in the 3' UTR of *ARRB2*, was also genotyped due to its previous associations with various dependences (Ikeda et al., 2007; Sun et al., 2008). Unfortunately, this SNP did not pass quality control measures for Taqman genotyping and was therefore removed from further analysis. Genotyping reactions of 5 μl total volume (containing 2 μl of DNA and 3 μl of Taqman® Genotyping Master Mix) were prepared in a 384-well plate format using a Biomek 3000 robotic workstation (Beckman Coulter, Inc.; Brea, CA). SNP genotyping was performed using an ABI 9700 and Taqman® SNP Genotyping Assays (Applied Biosystems Inc. (ABI); Foster City, CA, USA). For quality control purposes, 10% of samples were genotyped in duplicate. Following amplification, genotypes were acquired using ABI Prism® 7900 Sequence Detections System using SDS v2.2 software and Taqman® Genotyper Software v1.0 (ABI). Genotyping call rates for both populations were 99%.

Statistical analysis

The allelic and genotypic association of SNPs with opioid and cocaine dependence was determined using the Chi-square test in the software package PLINK v1.07 (Purcell et al., 2007). For each SNP, deviation from Hardy-Weinberg was assessed in the total population and also in cases and controls individually. Sliding-window haplotype analysis was performed in PLINK using the expectation maximization (EM) algorithm (http://pngu.mgh.harvard.edu/~purcell/plink/) (Purcell et al., 2007).

Results

Genotypic and allelic frequencies for each SNP in both opioid- and cocaine-dependent populations are reported in Tables 1 & 2. rs3786047, rs1045280, rs2271167 and rs4790694 were in Hardy-Weinberg Equilibrium (HWE) and rs4522461 (p=0.01) rs2036657 (p=0.05) deviated slightly in the control population. In comparing genotype and allele distributions between opioid-dependent and control samples, no statistically significant associations were detected (Table 1). Similarly, an allelic association was not detected when comparing the cocaine-dependent and controls samples; however, the genotypic association reached nominal significance for rs4522461 (p=0.05) (Table 2) as well as the 2 SNP haplotype (rs3786047 and rs4522461, p=.04). There were no additional statistically significant haplotype associations identified in either population (Supplemental Digital Content: Tables 1&2).

Discussion

This report focused on the potential association of *ARRB2* variants with cocaine or opioid dependence and our results, generated in a European-American population, suggest no association with risk for dependence on either drug. Interestingly, rs4522461 was nominally associated with cocaine dependence (p=0.05); however, this association may be spurious

since the SNP deviated from HWE in controls (p=.01). Also, considering the number of statistical tests conducted, this association would not remain significant after correction for multiple testing.

Previous studies have evaluated *ARRB2* variants in relation to other drugs of abuse. In a genetic case-control association study for both methamphetamine dependence and schizophrenia, *ARRB2* SNPs were genotyped in a Japanese population (547 schizophrenia patients, 177 methamphetamine-dependent patients and 546 controls). In this Japanese population, three of the *ARRB2* SNPs genotyped in our study (rs1045280, rs2036657, and rs4790694) were found to be nominally associated with methamphetamine dependence; no associations were found between *ARRB2* SNPs and schizophrenia (Ikeda et al., 2007). Sun *et al.* reported an association of SNPs in both *B*-arrestins 1 and 2 with nicotine dependence in European American smokers. In *ARRB2*, rs4790694 as well as a haplotype formed by SNPs rs3786047, rs4522461, rs1045280 and rs4790694 showed a significant positive association in the European American sample but no association in African Americans (n=2037 subjects from 602 nuclear families across both ethnicities (Sun et al., 2008). In our European American samples, these SNPs were genotyped but were not found to be associated individually or as a haplotype. Recently, Bousman, *et al.* (2010) conducted a case control association in 193 non-psychotic Caucasian males (117 methamphetamine-dependent and 76 controls) focused on confirming SNPs previously found to be associated with methamphetamine dependence in Asian populations including rs4790694, and found no evidence of significant association (Bousman et al.). Further, no association was detected for ARRB2 variants (including rs4522461 and rs3786047; both genotyped in the present study) genotyped on the Illumina array of 1536 SNPs for association with heroin addiction (n=412 former severe heroin addicts in methadone treatment and n=184 controls with no history of drug abuse) (Levran et al., 2008).Currently, the functional role of these genotyped SNPs has not been reported. Future analysis may include genotyping SNPs predicted to alter ARRB2 expression. rs34230287, located in the promoter region has been shown to alter expression of *B*-Arrestin 2 in neutrophils (Zhang et al., 2007). rs34230287, in addition to rs3786047, rs1045280, and rs2036657, were genotyped in a recent study analyzing *ARRB2* gene variants and the response to methadone in opioid-dependent patients. Interestingly, Oneda *et al.* reported that homozygosity for the minor alleles at rs3786047, rs1045280, and rs2036657 conferred a non-responding phenotype for methadone maintenance treatment (Oneda et al., 2011). These 3 SNPs were genotyped in the present study and although they were not found to be associated with opioid dependence may predict response to treatment.

It is of note that the samples genotyped in the present study were obtained from a shared repository and therefore it is possible that in the future, efforts may be duplicated when genotyping candidate genes of addiction. To our knowledge, besides the Levran et al. study mentioned in the latter, genotype data for ARRB2 has not been reported previously using the samples used in the present study(Levran et al., 2008).

In summary, polymorphisms in *ARRB2* were not shown to be associated with cocaine or opioid dependence in European American populations genotyped in this study. As this is one of the first studies to report results from a case-control association of *ARRB2* in opioid or cocaine dependent populations, further studies are needed to determine whether *ARRB2* may be relevant in other ethnic populations, may confer risk that is specific to methamphetamine or nicotine dependence in European Americans, or influence the pharmacogenetic response to treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Genotypic and allelic distributions for *ARRB2* in opioid –dependent and control samples

SNP	Genotypic Freq.			Genotypic p-values	Minor Allele Freq.	X^2	Allelic p-values
rs3786047							
Case	0.11 (AA)	0.46 (AG)	0.43 (GG)	0.78	0.34 (A)	0.029	0.86
Control	0.10 (AA)	0.48 (AG)	0.42 (GG)		0.34 (A)		
rs4522461							
Case	0.06 (TT)	0.38 (TG)	0.56 (GG)	0.36	0.25 (T)	0.043	0.83
Control	0.05 (TT)	0.42 (TG)	0.53 (GG)		0.26 (T)		
rs1045280							
Case	0.11 (CC)	0.46 (CT)	0.41 (TT)	0.67	0.35 (C)	0.227	0.63
Control	0.10 (CC)	0.48 (CT)	0.42 (TT)		0.34 (C)		
rs2271167							
Case	0.12 (AA)	0.46 (AG)	0.42 (GG)	0.67	0.35 (A)	0.205	0.65
Control	0.10 (AA)	0.48 (AG)	0.42 (GG)		0.34 (A)		
rs2036657							
Case	0.11(GG)	0.46 (AG)	0.42 (AA)	0.62	0.35 (G)	0.282	0.59
Control	0.09 (GG)	0.48 (AG)	0.43 (AA)		0.33 (G)		

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Table 2

Genotypic and allelic distributions for *ARRB2* in cocaine –dependent and control samples

SNP	Genotypic Freq.			Genotypic p-values	Minor Allele Freq.	X^2	Allelic p-values
rs3786047							
Case	0.12 (AA)	0.43 (AG)	0.45 (GG)	0.30	0.33 (A)	0.051	0.82
Control	0.10 (AA)	0.48 (AG)	0.42 (GG)		0.34 (A)		
rs4522461							
Case	0.05 (TT)	0.34 (TG)	0.61(GG)	**0.05**	0.22 (T)	3.522	0.06
Control	0.05 (TT)	0.42 (TG)	0.53 (GG)		0.26 (T)		
rs1045280							
Case	0.16 (CC)	0.42 (CT)	0.47 (TT)	0.17	0.32 (C)	0.587	0.44
Control	0.10 (CC)	0.48 (CT)	0.42 (TT)		0.34 (C)		
rs2271167							
Case	0.12 (AA)	0.41 (AG)	0.47 (GG)	0.14	0.32 (A)	0.520	0.47
Control	0.10 (AA)	0.47 (AG)	0.42 (GG)		0.34 (A)		
rs2036657							
Case	0.12 (GG)	0.41 (AG)	0.47 (AA)	0.13	0.33 (G)	0.138	0.70
Control	0.09 (GG)	0.48 (AG)	0.43 (AA)		0.33 (G)		