HHS Public Access

Author manuscript

Am J Addict. Author manuscript; available in PMC 2017 August 03.

Published in final edited form as:

Am J Addict. 2015 June ; 24(4): 329–335. doi:10.1111/ajad.12187.

Functional *Mu* Opioid Receptor Polymorphism (*OPRM1 A*^{118}G) Associated With Heroin Use Outcomes in Caucasian Males: A Pilot Study

Eric A. Woodcock, BS[1,2], **Leslie H. Lundahl, PhD**[1], **Margit Burmeister, PhD**[4], and **Mark K. Greenwald, PhD**[1,2,3]

[1]Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit Michigan

[2]Translational Neuroscience Program, Wayne State University, Detroit Michigan

[3]Department of Pharmacy Practice, Wayne State University, Detroit Michigan

[4]Departments of Psychiatry, Human Genetics and Computational Medicine and Bioinformatics, Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor Michigan

Abstract

Background—Heroin's analgesic, euphoric and dependence-producing effects are primarily mediated by the *mu* opioid receptor (MOR). A single gene, *OPRM1*, encodes the MOR. The functional polymorphism $A^{118}G$, located in exon 1 of the *OPRM1* gene, results in anatomically-specific reductions in MOR expression, which may alter an individual's response to heroin. In prior studies ^{118}G (rare allele) carriers demonstrated significantly greater opioid tolerance, overdose vulnerability, and pain sensitivity than ^{118}AA homozygotes. Those findings suggest *OPRM1* genotype may impact characteristics of heroin use.

Methods—The present pilot study characterized the impact of *OPRM1* genotype (rs1799971, ^{118}G allele carriers vs. ^{118}AA homozygotes) on heroin-use phenotypes associated with heroin dependence severity in a sample of male, Caucasian chronic heroin users (n = 86).

Results—Results indicate that ^{118}G allele carriers reported significantly more heroin use-related consequences and heroin-quit attempts, and were more likely to have sought treatment for their heroin use than ^{118}AA homozygotes.

Conclusions—These preliminary findings, consistent with extant data, illustrate a role for *OPRM1* allelic variation on heroin use characteristics, and provide support for considering genotype in heroin treatment and relapse prevention.

Address correspondence to Greenwald, Department of Psychiatry and Behavioral Neurosciences, Tolan Park Medical Building, 3901 Chrysler Drive, Suite 2A, Detroit, MI 48201. mgreen@med.wayne.edu.

Author Contributions: E.W. was responsible for conceptualizing and performing this data analysis, and drafting the manuscript. L.H.L. contributed to psychiatric screening and edited the manuscript. M.B. conducted genotyping analysis and edited the manuscript. M.K.G. contributed to study design, data coordination, and edited the manuscript. All authors have reviewed content and approved the final version for publication.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

INTRODUCTION

Mu opioid receptors (MORs) mediate most of the clinically salient effects of heroin (MOR agonist), including analgesia, euphoria, and depressed respiration.[1–3] MOR anatomical location and post-synaptic connectivity dictate the downstream effects of a bound agonist. A single gene, *OPRM1*, encodes the MOR.[4] Variants in the *OPRM1* gene can alter opioidergic function and may therefore impact an individual's response to opioid administration. A widely-studied *OPRM1* variant is a single nucleotide polymorphism (SNP) $A^{118}G$, rs1799971, resulting in an *Asn40Asp* amino acid change.[4] While the specific neurobiological effects of this SNP are not fully understood, data from rodent and human studies suggest the minor *Asp* allele is less physiologically functional, though findings to the contrary[5] exist. The ^{118}G variant is associated with diminished mRNA and protein levels in some brain regions.[6,7] Using whole brain quantitative autoradiography, Wang et al.[8] found diminished MOR expression in the 'pain matrix' (cingulate and insular cortices, amygdala and periaqueductal gray;[9–11]) and 'reward centers' (nucleus accumbens and ventral tegmental area) of the ^{112}GG homozygote mouse brain (mouse equivalent of human ^{118}GG homozygotes) compared to ^{112}AA homozygotes. Mague et al.[12] found less morphine-induced antinociception in ^{112}GG homozygous mice than ^{112}AA homozygotes. Further, human ^{118}G carriers report less morphine-induced analgesia[13–15] and hypersensitivity to nociceptive stimuli compared to ^{118}AA homozygotes.[15,16] Consistent with the above findings, Huang et al.[17] demonstrated diminished MOR protein expression in a rodent model of the ^{118}GG genotype, and Beyer et al.[18] and Kroslak et al.[19] each found human ^{118}G-variant cell lines demonstrated lower cell-surface MOR agonist binding capacity (lower B_{max}). Further, clinical studies using [^{11}C] carfentanil PET imaging found the ^{118}G* genotype was associated with diminished MOR receptor availability.[20,21]

Genetic association studies frequently attempt to link polymorphisms with initial vulnerability to drug dependence. Coller et al.[22] conducted a meta-analysis of 16 studies examining opioid dependent and control subjects (> 5000 subjects) and found no link between *OPRM1* rs1799971 genotype and opioid dependence. Arias et al.[23] conducted a meta-analysis of 22 published studies investigating risk of substance dependence by *OPRM1* rs1799971 genotype across ethnicities (>8000 subjects) and drugs of abuse (alcohol, heroin, opioids, and cocaine); they found no link between genotype and substance dependence, nor did they find any significant relationships between ethnicity, genotype and dependence. Haerian and Haerian[24] conducted a meta-analysis of 18 studies (>8000 subjects) and found no association between *OPRM1* rs1799971 genotype and opioid/cocaine or heroin dependence in African-American or Caucasian subjects, but opioid-dependent Asian subjects (among whom the ^{118}G variant is more prevalent: 40–50% vs. 15–30% in Caucasians and 1–3% in African-Americans;[25]) were more likely to be ^{118}G carriers than ^{118}AA homozygotes.

However, genetic factors likely influence all phases of drug dependence, not solely vulnerability to dependence.[26] Nikolov et al.[27] hypothesized that the ^{118}G variant may not impact risk for but, rather, severity of heroin dependence. In support of this hypothesis, heroin-dependent ^{118}G carriers demonstrated enhanced heroin tolerance (in haplotype with IVS2 +31 G/A variant;[28]) and 5.3 × greater risk of cardiac or respiratory arrest[29] than ^{118}AA

homozygotes. Diminished MOR expression in analgesia- and euphoria-mediating brain regions[8,30] may explain *118G* carriers' enhanced opioid tolerance[13–15,28] and pain sensitivity.[15,16] Exaggerated pain sensitivity and enhanced opioid tolerance may lead users to self-administer heroin via a more pharmacokinetically-efficient route (e.g., injection vs. insufflation), use more frequently, or consume larger doses to achieve the desired effects, thereby increasing risk of overdose and respiratory/cardiac arrest.[29]

In the present study, we examined heroin use phenotypes associated with heroin dependence severity by *A118G* genotype in chronic, regular Caucasian male heroin users not currently seeking treatment. Consistent with Nikolov et al.[27], we hypothesized *118G* carriers would report heroin use characteristics indicative of greater severity of heroin dependence including: more lifetime heroin use consequences (specifically overdose), lifetime heroin quit attempts, and frequent current heroin use, and greater likelihood of having sought treatment for their heroin use and self-administering heroin *via* injection than *118AA* homozygotes.

MATERIALS AND METHODS

Participants

This retrospective investigation utilized screening data obtained from four source studies approved by Institutional Review Boards at Wayne State University and the University of Michigan (for methodological details see: [31–34]), and was conducted in accordance with the Declaration of Helsinki (1964).[35] The National Institute on Drug Abuse issued certificates of confidentiality for these studies. Participants were recruited from the Detroit, Michigan metropolitan area using print media advertisements and word-of-mouth referral.

Individuals identifying themselves as regular heroin users and not seeking treatment completed a brief phone screen. Eligible individuals were scheduled for an in-person screening interview. Volunteers provided informed consent, demographic data, and comprehensive substance use and medical histories. Current heroin use was confirmed by opioid-positive urine sample (>300 ng/ml). Participants were sober (<.002% expired blood alcohol content) during the intake interview. Completion of the screening visit earned each participant a $30 check.

Genotyping

Plasma samples were collected (6 ml per participant) in EDTA tubes. Participant DNA was extracted using the Qiagen kit (formerly Gentra Puregene) and genotyped using the Taqman assay according to the manufacturer's conditions and solutions (Applied Biosystems ABI, Foster City, CA). Additionally, a subset of participant DNA samples were genotyped using Illumina Golden Gate addiction panel.[35] The two assays were in complete agreement for *OPRM1* rs1799971 genotype for this sample. The Golden Gate panel has the advantage of including 186 ancestry informative markers (AIMs) that were used to evaluate racial stratification and confirm self-reported racial identity from the full sample of source study participants, which included African- Americans and Caucasians only (n =186). Principal component analyses were conducted (forcing a two-factor solution with a Varimax rotation)

with the 150 AIMs containing at least 90% genotype data and a factor loading coefficient ≥. 30 which revealed complete separation between races and no overlapping cases (Fig. 1). These analyses supported the self-reported racial identities and indicated the presence of genetically-distinct groups.

A common *OPRM1* SNP occurs at position 118 (rs1799971) in exon 1 (adenine-to-guanine substitution: $A^{118}G$) encoding an asparagine-to-aspartic acid amino acid exchange (*N40D*) in the N-terminal domain.[4] Due to scarcity of the *OPRM1* ^{118}GG genotype and scarcity of the *G* allele in African-Americans, analyses presented herein contrasted Caucasian ^{118}G carriers (^{118}GG and ^{118}AG) with ^{118}AA homozygotes. Indeed, of the 131 African-American individuals available for analysis, only five were ^{118}G carriers: insufficient for outcome analyses.

Phenotyping

Heroin-use phenotypes were derived from a comprehensive, standardized self-report substance use history questionnaire routinely used in our laboratory. Analyses focused on five dependent variables: current heroin administration route (injection vs. non-injection), past-month heroin use frequency, lifetime number of heroin use-related consequences, lifetime number of attempts to quit using heroin, and having ever sought treatment for heroin use. Current route of self-administration, lifetime treatment for heroin use, and lifetime number of attempts to quit (with and without treatment) using heroin were assessed via single-item face-valid self-report variables. Past-month heroin use frequency was calculated as a product score of past-week mean daily use multiplied by number of days using heroin in the past month. Heroin use consequences were assessed *via* a 21-item questionnaire (see Table 2). Items parallel SCID symptom checklists and encompass potential heroin use-related consequences. Participants were asked to indicate (present/absent) each consequence they experienced as a direct result of their heroin use. Endorsed consequences were summed for analysis of total consequences (outcome measure); however, individual item endorsement was also explored to better understand the effects of $A^{118}G$ genotype on heroin use consequences.

Data Analyses

Distributions of continuous variables were evaluated for skewness and kurtosis[36] to assess normality prior to outcome analyses. The only non-normal distribution was lifetime heroin quit attempts (positively skewed), which was normalized using a square root transformation. Unequal sample sizes across genotype increased our risk of Type I error. To protect against Type I error inflation, Levene's Test of Equality of Error Variances was used to confirm (all *p* values >.50) homogeneity of variance for each outcome variable in our analyses.

All analyses were conducted using SPSS version 22 with the criterion to reject the null hypothesis set at $p \leq .05$. Fisher's Exact and Chi Square tests were performed to assess the distribution of genotype by route of heroin administration (injection vs. non-injection), seeking treatment for heroin use, and individual items in the heroin use consequences survey. Continuous variables (e.g., past-month heroin use frequency) were evaluated using one-way Analyses of Variance (ANOVAs) to compare genotype effects. Number of lifetime

heroin use consequences and quit attempts are likely to accumulate with longer duration of heroin use, which could bias interpretation of results. If these variables were positively correlated, analysis of covariance (ANCOVA), with years of heroin use entered as a covariate, was used in analyses. Descriptive statistics are presented as mean (M) ± one standard deviation (SD).

RESULTS

Participant Characteristics

All participants (n =86 Caucasian males) were current (opioid positive urine sample; >300 ng/ml) and chronic [M±1 SD=14.2±10.2 years] heroin users who were not currently seeking treatment. The average participant was 37.7±10.0 years old with 12.3±1.5 years of formal education. All participants reported regular heroin use, defined as >3 uses during the past week. ^{118}G carriers were significantly younger than ^{118}AA homozygotes, $F(1, 85)=6.28$, $p<.05$ [32.6 ± 9.7 vs. 39.1 ± 9.8 years old], but did not differ ($p>.25$) by years of education [12.7 ± 1.6 vs. 12.2 ± 1.5 years old].

Genotype Associated With Heroin Use Characteristics

Heroin use data are presented in Table 1. Fisher's Exact Test (FET) revealed current route of heroin administration (injection vs. non-injection) was not significantly associated with genotype [100% of ^{118}G carriers vs. 86.8% of ^{118}AA homozygotes injected heroin, p=.08; FET one-tailed; Cramer's V =.19 (small-to-moderate effect size)].

Chi-square analyses indicated ^{118}G carriers were significantly more likely (88.9% vs. 61.8%) to report having sought treatment for their heroin use at some point during their lifetime than ^{118}AA homozygotes [$\chi^2(1)=4.77$, $p<.05$]. Two thirds of participants (67.4%) reported seeking treatment for their heroin use, which was unrelated to duration of their heroin use, $F(1, 85)=0.93$, p=.34.

Past-month heroin-use frequency was not correlated with duration of heroin use ($r=-.15$; $p=.16$) and thus, ANOVA was used to evaluate the effect of genotype on use frequency. ^{118}G carriers did not report significantly different past-month heroin use than ^{118}AA homozygotes, $F(1, 84)=1.95$, $p=.17$ [126.8 ± 66.1 vs. 101.6 ± 68.5].

As expected, number of heroin quit attempts and years using heroin (duration) were positively correlated (r=.35, $p<.001$); thus, number of years using heroin was entered as a covariate. ANCOVA indicated genotype was significantly associated with heroin quit attempts, $F(1, 85)=3.92$, $p=.05$; partial *eta*-squared [η^2]=.045. ^{118}G carriers reported nearly twice as many heroin quit attempts as AA homozygotes [19.1 ± 30.4 vs. 11.0 ± 20.9].

Lifetime heroin use consequences were positively correlated with number of years using heroin (r=.39, p<.01); again, as anticipated, the latter variable was entered as a covariate in analyses. ANCOVA revealed genotype was significantly associated with heroin-use consequences, $F(1, 85)=4.47$, $p<.05$; $\eta^2=.051$. ^{118}G carriers reported more lifetime heroin use consequences than AA homozygotes [11.1 ± 4.2 vs. 9.2 ± 4.7].

Item-level endorsements of lifetime heroin use consequences are presented in Table 2. Chi-square analyses revealed item-level differences between genotypes: *118G* carriers endorsed 'overdose' (66.7% vs. 33.8%), 'seizure/fits' (16.7% vs. 2.9%), and 'high at work' (100.0% vs. 76.1%) significantly more frequently than *118AA* homozygotes [$\chi^2(1) = 6.36$, $p < .05$, $\chi^2(1) = 4.90$, $p < .05$, and $\chi^2(1) = 5.30$, $p < .05$; respectively]. Although every *118G* carrier in this sample endorsed they 'couldn't stop using' heroin, this item did not significantly differ by genotype [100.0% vs. 85.3%; $\chi^2(1) = 3.00$, $p = .08$]. No other items approached significance (p values >.10).

Behavioral Associations Unrelated to Genotype

Lifetime quit attempts and heroin use consequences were positively correlated ($r = .31$, $p < .01$). Number of heroin use consequences (but not quit attempts or use frequency, $ps > .10$) differed by current heroin administration route, $F(1, 85) = 11.67$, $p < .001$, while controlling for duration of heroin use. Those who currently injected heroin endorsed significantly more lifetime heroin use consequences than those who did not inject heroin [10.1 ± 4.5 vs. 5.7 ± 3.7].

DISCUSSION

The current study contrasted clinically-relevant heroin use characteristics by *OPRM1* rs1799971 genotype (*118G* carriers vs. *118AA* homozygotes) in a non-treatment-seeking sample of chronic, regular Caucasian male heroin users. We hypothesized *118G* carriers would report heroin use characteristics in support of Nikolov and colleagues[27] hypothesis that the *118G* allele is associated with more 'severe' opioid dependence. *118G* carriers reported more lifetime heroin-use consequences, quit attempts and were more likely to have sought treatment for their heroin use, relative to *118AA* homozygotes. However, there were no genotype differences in reported past-month heroin use frequency or current route of self-administration. These preliminary findings provide initial evidence that the *OPRM1 118G* variant may be associated with more burdensome outcomes from chronic heroin use.

118G carriers reported more lifetime heroin-use consequences than *118AA* homozygotes (endorsing ~11 vs. ~9 of the 21 possible consequences). Rather than being a simple count of potentially redundant episodes of dysfunctional behavior and adverse events, these data indicate *118G* carriers experienced a more expansive range of heroin use-related consequences. Clinical and preclinical studies[6–8,17,20,21,30] indicate the *118G* allele may be less physiologically functional, resulting in anatomically-specific diminished MOR availability associated with increased pain sensitivity and opioid tolerance.[13–16,28] Considering these findings, we hypothesized that heroin may be less potent or have lower intrinsic efficacy in *118G* carriers, who may therefore self-administer larger doses to achieve desired effects, thereby enhancing risk of overdose. We could not collect accurate data on heroin dosage so we were unable to test this hypothesis directly. However, item-level analyses of heroin use consequences confirm that *118G* carriers were more likely to report 'overdose' and 'seizures/fits' from heroin use than *118AA* homozygotes, providing indirect support for this hypothesis. These data are consistent with Manini et al.[29] indicating the *118G* variant conveyed a 5.3-fold greater risk of cardiac or respiratory arrest from heroin

overdose. ^{118}G carriers reported having been ‘high at work’ more frequently, which was unexpected, but consistent with the working hypothesis. Finally, ^{118}G carriers were not statistically (p =.08) more likely to report they ‘couldn’t stop using’ than ^{118}AA homozygotes, though a ceiling effect is possible (100% of ^{118}G carriers endorsed they ‘couldn’t stop using’ heroin).

^{118}G carriers reported significantly more lifetime attempts to quit using heroin than ^{118}AA homozygotes, controlling for years of heroin use. Given that study participants were current heroin users, these prior quit attempts were by definition unsuccessful. While these data cannot address the temporal (or causal) relationship between heroin-quit attempts and use consequences, these variables are significantly positively correlated. Moreover, ^{118}G carriers were significantly more likely to have sought past treatment for their heroin use than ^{118}AA homozygotes.

All ^{118}G carriers (100%) reported current self-administration of heroin via injection (vs. non-injection), but not statistically more than ^{118}AA homozygotes (86.8%; possible ceiling effect). Injection is a more efficient and dangerous drug delivery route compared to snorting or smoking, and is associated with more rapid progression to dependence,[37] more severe heroin dependence, quicker relapse, and worse opioid withdrawal symptoms.[38–40]

Some limitations of the present study are important to note. First, this pilot investigation used a small convenience sample. Thus, the present results should be interpreted with caution and would benefit from replication in a larger sample. However, the specific *a priori* selection of the $A^{118}G$ polymorphism for analysis, our hypothesis-driven analytic approach, demographic homogeneity of the sample, and moderate effect sizes compensated for the limited statistical power and revealed several significant differences by genotype. Second, while some of the present findings support Nikolov and colleagues[27] working hypothesis, these findings are not conclusive. Indeed, several of our hypotheses were not supported by the data: ^{118}G carriers did not report more frequent heroin use or higher rates of injection (possibly due to a ceiling effect). Third, reliance on self-report data is a limitation in the current study. Fourth, while some participants did report poly-substance use, and previous findings indicate the $A^{118}G$ polymorphism is related to alcohol use phenotypes, this sample is composed of primary heroin users and thus analyses focused solely on heroin use-related phenotypes. Finally, due to scarcity of the ^{118}G allele, we focused on a demographically-homogenous sample (Caucasian males) for three reasons. First, the $A^{118}G$ polymorphism is infrequent among African-Americans (only five ^{118}G carriers in our sample; 3.8%), which is consistent with the literature (1–3%;[25]). Second, meta-analyses indicate ethnicity may be related to dependence.[24] Third, extant research suggests there may be gender-specific effects of the $A^{118}G$ genotype on substance use characteristics,[41–43] pain threshold,[44] and opioid response.[12] Despite our interest in examining possible gender effects in heroin use characteristics, there were too few female ^{118}G carriers (n =7) available to address this issue. Finally, some findings presented here would not survive multiple comparison correction for the variants tested, and hence should be considered hypothesis-generating.

With these caveats in mind, the present findings offer initial support that $A^{118}G$ genotype may influence heroin use characteristics relevant to treatment efficacy in opioid dependent

individuals. ^{118}G carriers reported experiencing more heroin use consequences indicative of greater psychosocial dysfunction and possible health problems (e.g., ‘seizure/fits’, ‘high at work’, ‘overdose’), which may complicate and prolong treatment (i.e., necessitating a higher level of care). All ^{118}G carriers reported currently injecting heroin, thereby increasing risk of contracting blood borne viruses or developing infections from shared and/or unclean syringes. Finally, ^{118}G carriers were more likely to have sought treatment in the past and reported more lifetime attempts (i.e., prior failures) to abstain from heroin use, which may reflect greater susceptibility to relapse. Taken together, these findings highlight the importance of, and potential role for, considering *OPRM1* genotype in opioid dependence treatment.

Acknowledgments

NIH grant R01 DA015462 from the National Institute on Drug Abuse (to MKG), a research grant (Joe Young, Sr./ Helene Lycaki Funds) from the State of Michigan, and the Detroit Wayne Mental Health Authority supported this research. Data for this study were obtained under registered NIH clinical trials NCT00218309, NCT00218361, NCT00608504, and NCT00684840.

The authors thank Ken Bates for recruiting participants; and Debra Kish, Joi Moore and Lisa Sulkowski for data collection and management.

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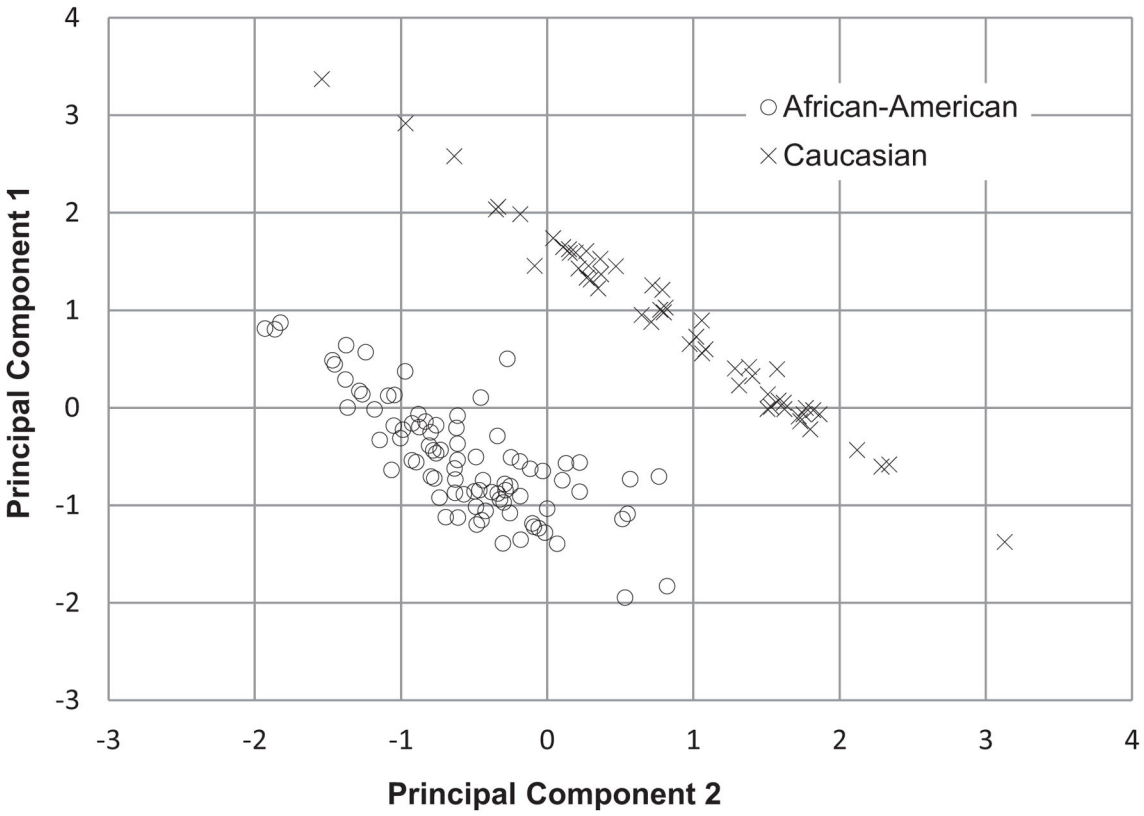

FIGURE 1.

Self-reported racial identification (African-American vs. Caucasian) stratified by principal component factor loading. Principal component analysis of the 150 ancestry informative markers (AIMs) with >90% genotype data for this sample and a factor loading coefficient ≥. 30 revealed complete separation between races. These analyses indicated that self-reported racial identity agrees with AIMs and argued against racial stratification being a primary study confound.

TABLE 1

Heroin use characteristics

	^{118}AA (n =68) M (± 1 SD)	^{118}G* (n =18) M (± 1 SD)	F or χ^2	Cohen's d
Age at First Use	24.4 (7.2)	20.9 (4.4)	3.78	0.53
Years of Use	14.8 (10.4)	11.7 (9.2)	1.32	0.31
Use Frequency	101.6 (68.5)	126.8 (66.1)	1.95	0.37
Use Consequences#	9.2 (4.7)	11.1 (4.2)	4.47*	0.42
Quit Attempts#	11.0 (20.9)	19.1 (30.4)	3.92*	0.35
Route (% inject)	85.3%	100.0%	2.66	–
Sought Treatment (%)	61.8%	88.9%	4.77*	–

#Indicates ANCOVA was performed with duration of heroin use entered as covariate.

Significant differences indicated: *$p \leq .05$.

TABLE 2

Heroin use consequences item endorsement

Item (% Endorsed)	Overall (*n* =86)	^{118}AA (*n* =68)	$^{118}G^{*}$ (*n* =18)	χ^2
Instructions: In your opinion, have you had any of these problems because you took heroin? If you have, please mark each below:				
Unexpected reaction	35.3%	32.8%	44.4%	0.84
Overdose	40.7%	33.8%	66.7%	6.36 *
Memory lapse	31.4%	32.4%	27.8%	0.14
Seizure/fits	5.8%	2.9%	16.7%	4.90 *
Shakes/tremors	31.8%	32.4%	29.4%	0.05
Couldn't stop using	88.4%	85.3%	100.0%	3.00
Arrested/legal problems	45.3%	45.6%	44.4%	0.01
Accident/injury	17.4%	19.1%	11.1%	0.63
Health problem	30.2%	30.9%	27.8%	0.07
High at work	81.2%	76.1%	100.0%	5.30 *
Lost job	57.6%	55.2%	66.7%	0.76
Missed work	67.4%	64.7%	77.8%	1.11
Got warning or disciplined at work	43.0%	41.2%	50.0%	0.45
High at school	25.6%	22.1%	38.9%	2.12
Missed school	20.9%	17.6%	33.3%	2.12
Suspended or expelled from school	10.5%	10.3%	11.1%	0.01
Fight or quarrel	33.7%	29.4%	50.0%	2.70
Drove under influence	87.2%	85.3%	94.4%	1.07
Family problems	87.2%	85.3%	94.4%	1.07
Financial problems	95.3%	95.6%	94.4%	0.04
Visited Emergency Room	34.3%	32.7%	40.0%	0.28

* Indicates significant difference between OPRM1 118AA and 118G carrier genotypes ($p < .05$).