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Variation in *OPRM1* and Risk of Suicidal Behavior in Drug-Dependent Individuals

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Abstract

Completed suicide and non-fatal suicide-related outcomes (SRO), such as suicidal ideation and attempts, are heritable. Hishimoto et al. (2008) reported a protective effect of the G allele of Asn40Asp (rs1799971) on risk for completed suicide. We examined the association of three *OPRM1* SNPs (rs1799971, rs609148 and rs648893) with SRO in 426 European-Americans, using GEE logistic regression analysis to examine the association of a lifetime history of SRO. There was no allelic association with the SRO phenotypes. A larger sample may be needed to identify risk variants that convey SRO risk. *OPRM1* may not be important in the risk of SRO.

Introduction

Suicide is a prevalent public health problem, with an annual worldwide incidence of approximately 1 million, making it the tenth leading cause of death.¹ The occurrence rate of non-fatal, suicide-related outcomes (SROs) (e.g., suicidal ideation, gestures, and attempts, irrespective of the severity of the attempt or the degree of intent²) is estimated to be 10-40 times that of completed suicide.³ A study comparing suicide rates in two large epidemiologic studies conducted 10 years apart in the United States, the National Longitudinal Alcohol Epidemiologic Survey (NLAES) and the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC), estimated the lifetime prevalence of suicide attempts to be 2.4%. The estimate was the same in both studies, however, it should be noted that, in the NESARC, only individuals that responded affirmatively to the survey questions for depressive episodes were queried about suicidal behaviors. Thus the

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comparison of the two studies was limited to respondents who initially screened positive for depression.⁴ The estimated lifetime prevalence for suicide attempts in the National Comorbidity Survey (NCS) was 4.7%,⁵ approximately twice that of the study comparing NLAES and NESARC. The World Mental Health Survey estimated the lifetime prevalence of suicide attempts to be 2.7% worldwide.⁶ The NCS and the National Comorbidity Survey Replication, also conducted 10 years apart, estimated the 12-month prevalence of suicide attempts to be 0.4 and 0.6%, respectively.⁷

Psychiatric and addictive disorders are important risk factors for both suicide attempts and completed suicide. The acute effects of alcohol increase the lethality of suicide attempts.⁸⁻¹¹

Completed suicide, a complex phenotype, has been shown to be heritable. A meta-analysis of twin studies showed significantly greater concordance for suicide in monozygotic than dizygotic twins and an estimated heritability of 21.9%.¹² Estimates of the heritability of SROs are more variable, ranging from approximately 17-55%.¹²⁻¹⁴ Although the inherited risk of SROs and completed suicide is largely independent of the inherited risk for psychiatric disorders, the latter may partially mediate suicidal behavior. Impulsive aggression, or the propensity to act on suicidal ideation, is an endophenotype of major significance in the genetic transmission of risk for suicide,^{15,16} while many patients with psychiatric illness, including mood disorders, never attempt suicide.⁸

Disturbances in a number of brain neurotransmitter systems, including the endogenous opioid system may contribute to the pathophysiology of suicidal behavior by modulating the brain's response to stress, which appears to be altered in individuals manifesting suicidal behavior.^{8,17} Post-mortem studies of suicide completers show a decreased concentration of opioid peptides,¹⁸ increased radioligand binding density of the mu-opioid receptor,^{19,20} increased mRNA expression of *OPRM1* (the gene that encodes the mu-opioid receptor),²¹ and altered binding affinity of the mu-opioid receptor (with individuals committing suicide having more high affinity receptors in the prefrontal cortex and more low affinity receptors in the precentral and postcentral gyri compared to controls.²²)

A genome-wide linkage scan of completed suicide in individuals with bipolar disorder identified a significant signal at 6q25.2.²³ *OPRM1* is approximately 230 kb from this region, and appears to fall within the 1-lod linkage support region for the D6S2436 marker linked to completed suicide.^{23,24} The most widely studied polymorphism in *OPRM1* is A118G (rs1799971), which encodes an amino acid (Asn40Asp) substitution.

Considerable evidence from *in vitro*, postmortem, and human laboratory studies supports the hypothesis that the Asn40Asp SNP is functional.^{25,26} Of particular relevance to the risk of suicide, human laboratory studies show that the Asn40Asp SNP moderates the cortisol response to naloxone^{27,28} and the stress response.²⁹

Hishimoto et al.²⁴ found that, of four *OPRM1* SNPs analyzed, Asn40Asp was the only one that was nominally significantly associated with suicide in a Japanese sample. The finding was consistent with a dominant model of inheritance, with the Asp40 allele having a protective effect. After controlling for sex and age, they found that the odds ratio (OR) for suicide associated with the Asp40 allele was 0.628, [95% confidence interval (95% CI) = 0.422-0.933], which is the equivalent of Cohen's $d = -0.257$.³⁰ Haplotype analysis of Asn40Asp and two of the other SNPs that were in tight linkage disequilibrium with it showed no significant association with completed suicide, suggesting that the Asn40Asp SNP is itself responsible for the association. The authors provided no information on psychiatric diagnoses in the sample.

We examined the association of three *OPRM1* SNPs with suicidal behavior in a sample of subjects with drug dependence, in an attempt to replicate and extend the findings of Hishimoto et al.²⁴ We hypothesized that there would be a lower prevalence of the Asp40 allele among individuals with a lifetime history of suicidal behavior compared to those without such a history. In this analysis, we controlled for potential confounding factors, including age, sex, and a co-occurring lifetime diagnosis of a major depressive episode (MDE).

Methods

Study Sample

The study sample included 434 subjects ascertained as affected sibling pairs for studies of the genetics of cocaine and opioid dependence.^{31,32} Subject recruitment and assessment were conducted at the University of Connecticut Health Center, Yale University, McLean Hospital and the Medical University of South Carolina. We included only subjects of self-reported European ancestry because of the prevalence of the Asp40 allele in that population is substantially higher than in African-Americans, the other major group recruited for these studies.³³ The sample comprised probands and self-identified full sibs, all of whom met DSM-IV criteria for cocaine and/or opioid dependence. Probands, but not siblings, were excluded from participation if they had a prior clinical diagnosis of schizophrenia or other psychotic disorder by self-report.

Phenotypic Assessment

The Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA, which is described in detail elsewhere^{34,35}) was used to identify the presence of DSM-IV diagnoses of substance use disorders, mood disorders, and anxiety disorders, as well as a lifetime history of suicidal and parasuicidal behaviors. All subjects were administered a section of the SSADDA that focused on suicidal behaviors, and its administration was not contingent upon affirmative responses to screening questions for the depression section of the interview. As part of the SSADDA interview, all subjects were asked whether they had ever thought about killing themselves, ever attempted to kill themselves, or ever harmed or mutilated themselves without intending to end their lives. Subjects responding in the affirmative to those questions were queried regarding additional self-damaging behaviors.

Genotyping

We examined three *OPRM1* SNPs: rs1799971, rs609148, and rs648893. Rs1799971 was chosen based on its prior association with suicide²⁴ and because it is in linkage disequilibrium (LD) with SNPs in a haplotype of *OPRM1*.³⁶ Because rs609148 and rs648893 are in a high degree of (LD) with SNPs from a second *OPRM1* haplotype,³⁶ they were chosen to represent this haplotype. These three *OPRM1* SNPs cover a large amount of the variation in *OPRM1* without being redundant. Subjects were genotyped as described previously in Zhang et al.³⁶

Statistical Analysis

Generalized estimating equations (GEE) logistic regression³⁷ was used to examine the effect of each of the three *OPRM1* SNPs separately on three suicidal phenotypes that are of increasing severity: suicidal ideation, a suicide plan, and attempted suicide, controlling for age, sex, and a comorbid lifetime diagnosis of MDE. Correlation among siblings was modeled by an exchangeable correlation structure in GEE logistic regression. Additive, recessive, and dominant models of inheritance of the minor alleles were considered for each phenotype.

Results

Demographic Characteristics

Subjects' mean age was 36.4 years (SD=8.7). The sample included 199 women (45.9%). Two hundred six subjects (48.7%) had at least one “independent” MDE (i.e., the episode was not thought to be caused by substance use) or “substance-induced” MDE (i.e., the episode was likely attributable to substance use), as determined by the SSADDA interview.³⁸ Of the 206 subjects with a lifetime history of an MDE, 165 (80.1%) had an MDE that was either substance-induced or due to bereavement and 41 (19.9%) had an independent depressive episode (i.e., Major Depressive Disorder). Suicidal ideation was reported by 221 individuals (50.9%), 106 (24.4%) had had a suicide plan, and 79 (18.2%) had attempted suicide. The number of substances on which individuals met criteria for a lifetime substance use disorder (abuse or dependence) ranged from 1-8 [mean = 4.33 (SD = 1.55)].

Allele Frequencies and Hardy-Weinberg Equilibrium

Table 1 shows the allele frequencies and exact tests for deviation from Hardy-Weinberg Equilibrium (HWE) for the three SNPs examined.³⁸ There was no evidence that any of the SNPs deviated from HWE in our study sample. The observed allele frequency for the Asp40 allele was within the expected range for a European-American sample.³³

Tests of Association with Suicidal Behavior

As shown in Table 2 χ^2 analysis showed no significant association with phenotype for either *OPRM1* alleles or genotypes. Table 3 shows similar results for the GEE logistic regression analysis controlling for age, sex, and lifetime MDE, examining additive models. Similar findings were obtained for dominant and recessive models (data not shown). Although a history of MDE was highly correlated with suicidal phenotypes, no SNP was significantly associated with phenotype in any of the models. A history of a suicide plan was significantly more common among males [OR = 2.15 (95% CI = 1.30, 3.56), $p < 0.003$]. After controlling for sex, among individuals with a lifetime history of MDE, the estimated OR (95% CI) of suicidal ideation or a suicide plan or attempt was 4.55 (3.08, 6.71), $p < 0.0001$; 3.59 (2.17, 5.94), $p < 0.0001$; and 3.37 (1.93, 5.87), $p < 0.0001$, respectively.

Because MDE was highly correlated with all three phenotypes, we also performed a *post hoc* analysis that included the interaction of genotype by MDE (shown in Table 3). There was not a significant interaction effect for genotype by MDE in any of the models.

Discussion

We found no evidence that any of the *OPRM1* SNPs that we examined was associated with suicidal behavior. In the absence of evidence of association, we did not perform a haplotype analysis. Hishimoto and colleagues²⁴ found a significant association only with alleles of Asn40Asp and no haplotypic association.

Reasons for our failure to replicate the findings of Hishimoto et al.²⁴ include the possibility that the phenotypes we examined (i.e., suicidal ideation, a suicide plan, and a suicide attempt) were not as severe as and possibly less heritable than the one studied by Hishimoto et al.²⁴ (i.e., completed suicide). Hence, our sample may not have provided adequate statistical power to detect an association. From the study by Hishimoto et al.,²⁴ where the probabilities of completed suicide by individuals with the AA genotype compared with G allele carriers was 0.418 and 0.292, respectively,³³ controlling for sibling correlation,³⁹ our study had 74% power to detect a difference at $p < 0.05$. Although providing fair power to

detect an association with that SNP, we did not examine all of the variation in *OPRM1*, so we cannot exclude the possibility that other variants in the gene are associated with risk of suicidal behavior. Excluding the promoter region, *OPRM1* is 200 kb in length of which the SNPs we examined span the distal 78 kb. Information from the HapMap project suggests these three SNPs are located in two haplotype blocks, but there are at least four in the *OPRM1* coding region in European Americans (<http://www.hapmap.org>). Further, population-specific, gene-gene interactions and epigenetic factors could also have obscured an association in our sample. Environmental factors affecting expression of suicidal behavior in drug users may also differ with those in other groups. Finally, the finding by Hishimoto et al.²⁴ could be spurious. Using an exact HWE test,³⁸ we found significant deviation from HWE for the Asn40Asp SNP in the control group from the study by Hishimoto et al.²⁴ ($p = .004$), in which the frequency of the G allele was higher than in the completed suicide group. This could reflect confounding by population stratification, genotyping error, or other potential biases.^{40,41} This type of error has been found to occur in about 7% of reports in high profile genetics journals.⁴⁰

As might be expected, we found that a history of MDE was strongly associated with the three suicidal behaviors examined, highlighting the importance of controlling for a history of MDE in genetic association studies of suicidal behavior. Women tend to attempt suicide more than men,⁵ although because they use less lethal methods they have a lower likelihood of completing suicide. In our analysis, men were more likely to have made a suicide plan. Although the small sample size limits interpretation of this finding, the effect of sex on suicidal behavior in drug-dependent individuals may differ from that in the general population.

Large, prospective cohort studies in high-risk patients are needed. These studies should control for potential confounds such as co-occurring mood disorders. Because suicidal behavior is particularly common in patients with substance dependence, additional research on genetic predictors of SROs and completed suicide in this patient population is warranted.

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Table 1
Allele and genotype frequencies

Allele/Genotype	<i>OPRM1</i> Single Nucleotide Polymorphisms		
	rs1799971 (N = 433)	rs609148 (N = 434)	rs648893 (N = 434)
A	0.886	0.247	0.757
G	0.114	0.753	0.243
AA	0.781	0.051	0.564
AG	0.210	0.392	0.385
GG	0.009	0.558	0.051
Exact HWE p-value	0.633	0.302	0.433

Table 2

Allele and genotype frequencies for three suicide-related phenotypes (p-values are for χ^2 unless noted otherwise).

SNP	Allele/Genotype	Suicidal thought			Suicide plan			Attempted suicide		
		Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
RS1799971	N	221	204		106	318		79	345	
	A	0.880	0.892	0.580	0.892	0.883	0.745	0.892	0.884	0.766
	G	0.120	0.108		0.108	0.117		0.108	0.116	
	AA	0.774	0.789	0.751*	0.793	0.776	0.908*	0.798	0.777	0.702*
	AG	0.213	0.206		0.198	0.215		0.190	0.216	
	GG	0.014	0.005		0.009	0.010		0.013	0.009	
RS609148	Exact HWE p-value	1.0000	0.4796		1.0000	0.7831		1.0000	0.5973	
	N	221	205		106	318		79	346	
	A	0.251	0.244	0.807	0.250	0.247	0.927	0.234	0.250	0.677
	G	0.749	0.756		0.750	0.753		0.766	0.750	
	AA	0.054	0.049	0.960	0.038	0.057	0.598	0.038	0.055	0.826
	AG	0.394	0.390		0.425	0.381		0.392	0.390	
RS648893	GG	0.552	0.561		0.538	0.563		0.570	0.555	
	Exact HWE p-value	0.5925	0.5689		0.2969	0.7838		0.5391	0.5659	
	N	221	205		106	318		79	346	
	A	0.749	0.763	0.621	0.750	0.758	0.818	0.766	0.754	0.762
	G	0.251	0.237		0.250	0.242		0.234	0.246	
	AA	0.552	0.576	0.879	0.538	0.572	0.521	0.570	0.564	0.827
RS648893	AG	0.394	0.375		0.425	0.371		0.392	0.381	
	GG	0.054	0.049		0.038	0.057		0.038	0.055	
	Exact HWE p-value	0.5925	0.6996		0.2969	1.0000		0.5391	0.6645	

* Fisher's Exact Test

Table 3
P-values for Wald type 3 GEE logistic regression by phenotype

	Suicidal Behavior Phenotype		
	Ideation	Plan	Attempt
Age	0.696	0.720	0.845
Sex	0.221	0.0028	0.656
Rs1799971 (G)	0.422	0.633	0.770
MDE	< 0.0001	< 0.0001	< 0.0001
Age	0.699	0.705	0.831
Sex	0.225	0.0032	0.675
Rs609148 (A)	0.760	0.956	0.883
MDE	< 0.0001	< 0.0001	< 0.0001
Age	0.694	0.708	0.835
Sex	0.229	0.0032	0.677
Rs648893 (G)	0.575	0.859	0.970
MDE	< 0.0001	< 0.0001	< 0.0001

Note: The results of the additive models are shown; results from recessive and dominant models were similar.