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No Association of COMT Val158Met Polymorphism with Suicidal Behavior or CSF Monoamine Metabolites in Mood Disorders

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Abstract

The Met allele of the Catechol-O-Methyltransferase (COMT) gene functional polymorphism (COMT-V158M) is associated with lower enzymatic activity than the Val allele and is reported to be associated with aggression, depression, and suicidal behavior. Since depression and impulsive-

aggressive behavior may mediate risk for suicidal behavior, we assessed the association of this polymorphism with suicidal behavior. Clinical (impulsive aggression) and biological (CSF monoamine metabolites) endophenotypes were tested as potential mediators of the effect of genotype on suicide risk. Subjects with mood disorders (N=486) and healthy volunteers (N=119), all European Caucasian, were genotyped for COMT-V158M and assessed for DSM IV diagnoses, lifetime suicidal behavior, lifetime impulsivity, hostility, and aggression. CSF monoamine metabolites were assayed in a sub-sample of mood disorder patients (N=111). We found no association between genotype and mood disorder diagnosis or with reported history of suicide attempt in mood disorder subjects. There was no association between genotype and lethality or method of suicide attempt, or with aggressive/impulsive traits. Further, there was no difference in monoamine metabolites by genotype. The COMT-V158M polymorphism was not associated with suicidal behavior in a Caucasian sample of mood disorder subjects, or with possible clinical or biological endophenotypes.

Keywords

aggression; catechol o-methyltransferase; depression; genetics; mood disorders; suicide

INTRODUCTION

Suicide accounts for almost 30,000 deaths a year in the US, mostly the result of mood disorders (Cavanagh, Carson, Sharpe et al., 2003; Center for Disease Control, 2007). Genetic factors contribute to the risk of suicidal behavior. Pooled data from 7 twin studies found concordance rates for suicide or suicide attempt are 23.5% in monozygotic twin pairs and 0.13% in dizygotic twins (Baldessarini & Hennen, 2004). Adoption studies demonstrate higher suicide rates in the biological parents than in adoptive parents of adoptees who died by suicide (Schulsinger, Kety, Rosenthal et al., 1979). However, the specific genes that contribute to vulnerability for suicidal behavior are unknown. One candidate gene in the study of suicidal behavior is the gene encoding the enzyme catechol-o-methyl-transferase (COMT). COMT is a major catabolic enzyme for catecholamine neurotransmitters in the brain.

COMT activity is affected by a single nucleotide polymorphism (SNP) at codon 158 (COMT-V158M) (Lachman, Papolos, Saito et al., 1996). The allele encoding a valine residue (Val allele) is associated with higher enzymatic activity compared with the allele encoding a methionine residue (Met allele), with 40% higher activity in Val/Val genotypes compared to Met/Met genotypes due to the lesser thermolability of the Val allele generated protein (Chen, Lipska, Halim et al., 2004).

The low-activity Met allele has been associated with major depression (MDD) in a Chinese sample (Li, Vallada, Curtis et al., 1997), and bipolar disorder (BD) in a Japanese sample (Ohara, Naga, Suzuki et al., 1998). In Caucasian samples associations have been reported with MDD in women only (Mynett-Johnson, Murphy, Claffey et al., 1998), rapid cycling BD patients (Kirov, Murphy, Arranz et al., 1998), and BD comorbid with panic disorder (Rotondo, Mazzanti, Dell'Osso et al., 2002). Most studies find no association with mood disorders or schizophrenia (Biomed European Bipolar Collaborative Group, 1997; Cusin, Serretti, Lattuada et al., 2002; Kirov, Jones, McCandless et al., 1999; Lachman, Kelso, Marino et al., 1997; Mynett-Johnson, Murphy, Claffey et al., 1998; Ohara, Nagai, Suzuki et al., 1998; Shifman, Bronstein, Sternfeld et al., 2004; Tunbridge, Burnet, Sodhi et al., 2004).

Recent meta-analysis of 519 cases and 933 controls from 6 studies found suggestive evidence of an association between COMT-V158M polymorphism and suicidal behavior,

perhaps related to the lethality of suicide attempt (Kia-Keating, Glatt, & Tsuang, 2007). Supporting this, are reports of association in schizophrenia between the low functioning Met allele and impulsive aggression (Kotler, Barak, Cohen et al., 1999; Lachman, Nolan, Moore et al., 1998; Strous, Bank, Parsia et al., 1997) and violent suicide attempts (Nolan, Volavka, Czobor et al., 2000), and the Met/Met genotype is associated with outward directed aggression in suicide attempters of varied psychiatric diagnosis (Rujescu, Giegging, Gietl et al., 2003). A post mortem study in suicide victims found the high-activity Val allele less prevalent and the heterozygote Val/Met more prevalent in male suicides than in controls (Ono, Shirakawa, Nushida et al., 2004). Other studies did not find evidence of an association between increased aggression and the Met allele (Baud, Courtet, Perroud et al., 2007; Hallikainen, Lachman, Saito et al., 2000; Jones, Zammit, Norton et al., 2001; Liou, Tsai, Hong et al., 2001; Russ, Lachman, Kashdan et al., 2000; Wei & Hemmings, 1999; Zammit, Jones, Jones et al., 2004).

In this study we examine COMT-V158M genotype with respect to suicidal behavior in mood disorder patients, including examination of carefully quantified intermediate psychopathological phenotypes. We hypothesize that mood disorder subjects with the Met allele will have higher levels of impulsivity and aggression and therefore be more prone to suicide attempts, particularly violent attempts. Moreover, as COMT is a major catabolic enzyme for catecholamine neurotransmitters, in a sub-sample of mood disorder subjects we evaluated CSF monoamine metabolite levels as potential biological endophenotypes for suicidal behavior.

METHODS

Subjects

A total of 605 subjects participated in the study. Mood disorder subjects (N=486) were recruited from clinics of a university affiliated psychiatric research institute and healthy volunteers (N=119) through advertisements and clinician referrals. Only Caucasian subjects of European origin were included in this analysis to reduce ethnic variation and stratification effects (Sabol, Hu, & Hamer, 1998).

Subjects were physically healthy on medical evaluation, negative for illicit drugs on toxicology screen and the subgroup that had CSF monoamine metabolites assayed were free from drugs known to affect monoamine turnover for at least two weeks (longer for longer half-life medications, such as six weeks for fluoxetine). Toxicology screen included blood and urine. Written informed consent was obtained as approved by the Institutional Review Board.

Clinical Assessment

DSM-IV Axis-I and II diagnoses were made using the Structured Clinical Interview for DSM IV, SCID-I/P (First, Spitzer, Gibbon et al., 2002) and II (First, Spitzer, Gibbon et al., 1996). Interviews were conducted by clinical psychologists with at least a Master's level degree. Diagnoses were determined at a consensus conference utilizing data from the SCID, psychiatric clinical evaluation, and medical records.

Lifetime aggression was rated using the Brown-Goodwin Aggression Scale (Brown & Goodwin, 1986b); lifetime hostility with the Buss-Durkee Hostility Inventory (Buss & Durkee, 1957); and impulsivity with the Barratt Impulsiveness Scale (Barratt, 1965). Beck's Medical Lethality Scale (Beck, Beck, & Kovacs, 1975) assessed the degree of medical injury resulting from suicide attempts with scores ranging from 0 for minimal medical damage to 8 for completed suicide. Attempts rating 4 or higher were designated high-lethality, as a score of 4 indicates that medical inpatient treatment for the sequelae of the

attempt was required. Suicidal ideation was assessed with the Scale for Suicide Ideation (Beck, Kovacs, & Weissman, 1979). For the analysis of severity of suicide attempts, we used the rating of the *most severe* suicide attempt each subject reported (designated here as maximum lethality). Suicide attempts carried out by overdose of sedative and non-sedative medication were categorized as non-violent. Attempts involving firearms, drowning, cutting, jumping, or hanging were categorized as violent.

Cerebrospinal Fluid Monoamine Neurotransmitter Metabolites

Lumbar puncture was performed on a sub-sample of drug-free mood disorder subjects (N=96) at approximately 8:00 a.m. after bed rest and fasting from midnight. Cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA), 3-methoxy-4-hydroxy-phenylglycol (MHPG) and homovanillic acid (HVA) were assayed by high-performance liquid chromatography as previously described (Placidi, Oquendo, Malone et al., 2001).

Genotyping

PCR was performed in a 20 μ l reaction mixture containing 40–100 ng DNA; 1 $\times$ PCR buffer; 0.2mM dXTP; 2mM MgCl₂; 4% of DMSO (Dimethyl sulfoxide) and 0.01% BSA; 50 ng of two primers, MCOMT-1F: 5'-CATGGCCCCGCTGCTGTC-3' and MCOMT-1R: 5'-AGGGGCCTGGTGATAGTGGGTTTT-3'; and 1 U of RedTaq polymerase (Sigma, St. Louis, MO USA). The reaction conditions were as follows: 94°C for 5min, 35 cycles at 94°C for 30s, 61°C for 30s and 72°C for 40s and a final extension step at 72°C for 4min. All PCR amplifications were performed in a DNA Robocycler (Stratagene, La Jolla, CA, USA). PCR products were then digested with Nla III restriction enzyme (BioLabs, USA) for 3 hours. Digested PCR products were electrophoresed on a 2.5% NuSieve[®] 3:1 agarose gel (BMA, Rockland, ME, USA) and visualized with UV light.

Statistical Analysis

Chi² test or Fisher's Exact test were used to compare genotypic frequencies between groups. Student's t-test was used to compare maximum lethality to suicide attempt by genotype. Tests were two-tailed and results are reported as mean and SD.

To investigate the relationship between genotype and clinical variables in mood disorder subjects we used general linear models. In each instance the clinical measure was the dependent variable, and COMT-V158M genotype, age, and sex were independent variables. The model analyzing state dependent suicidal ideation was restricted to mood disorder subjects who were in a current episode at time of assessment (N=256, 82%).

For biological measures, 3 GLMs were constructed with CSF 5-HIAA, MHPG, and HVA level as the dependent variable, and COMT-V158M genotype, sex, and age as the independent variables.

RESULTS

The mood disorder group had more females (66.9% vs. 36.1%, $\chi^2=39.9$, df=1, $p<.001$), but was not different in age from the control group (41.2 ± 11.8 vs. 41.6 ± 15.4 years, $t=.041$, df=603, $p=.967$). Primary diagnoses in the mood disorder group were: major depressive disorder N=365 (75.1%); bipolar disorder I N=61 (12.6%); and bipolar disorder II N=20 (12.3%). N=210 (43.3%) had a past substance use disorder diagnosis, not active in the six months prior to assessment, and N=213 (43.8%) a lifetime Axis II diagnosis. No differences were found in genotype distribution across Axis I diagnostic groups (Table 1), therefore, they were combined for subsequent analyses.

Subjects with a history of suicide attempt (N=201) had a mean maximum lethality of 3.4 ± 1.9 . Suicide attempt lethality rating scores had a normal distribution. Mean number of suicide attempts was 2.4 ± 1.6 . Methods used for the most lethal lifetime suicide attempt by non-violent methods were: sedative overdose N=102 (63.8%) and non-sedative drug/other substance overdose N=29 (18.1%). Violent methods utilized were: firearms N=2 (1.3%), immolation N=1 (.6%), cutting 19 (11.9%), jumping N=4 (2.5%), and hanging N=2 (1.3%). There was no difference by sex in violent or non-violent suicide attempt method (females 17%, males 19%, $\chi^2=0.116$, df=1, $p=0.73$).

Genotype Frequencies

For controls, the genotypes were in Hardy Weinberg equilibrium ($\chi^2=1.9$, df=1; $p=0.168$). Table 1 presents genotype frequencies for the three genotypes, and for Met allele genotypes compared to no Met allele genotype (Val/Val). Genotype frequencies did not differ between mood disorder and control groups, or between suicide attempters and non-attempters within the mood disorder group (Table 1). Among suicide attempters, there was no difference in use of violent method or in high vs. low-lethality of suicide attempts by genotype (Table 1).

Clinical Ratings of Suicide-related Measures

There was no effect of genotype on scores on rating scales for lifetime aggression, hostility, impulsivity in mood disorder subjects, or on recent suicidal ideation in currently depressed subjects (Table 2).

CSF Monoamine Metabolites

There were no genotype differences in CSF 5-HIAA, MHPG, and HVA levels controlling for age and sex (Table 2).

DISCUSSION

We found no association between the COMT-V158M polymorphism and MDD or bipolar disorder, or history of suicide attempt in mood disorder subjects. Others suggest, based on metaanalysis of studies of COMT-V158M and suicidal behavior, that the effect of this polymorphism on suicidal behavior may be related to the lethality of suicide attempts rather than risk for attempting suicide per se (Kia-Keating, Glatt, & Tsuang et al., 2007). Contrary to this suggestion, we did not observe any genotype differences with respect to lethality of suicide attempts or violence of method of attempt.

Nolan and colleagues found the Met allele to be more frequent in male (but not female) schizophrenic and schizoaffective patients who had made violent suicide attempts (Nolan, Volavka, Czobor et al., 2000), and Ono et al. found the Val/Val genotype absent in male suicides compared to male controls (Ono, Shirakawa, Nushida et al., 2004). These two studies suggest that the effect may be confined to males. Interestingly, Baud et al. report the opposite: in females, the Val/Val genotype associated with greater trait anger and risk of suicide attempt, particularly violent suicide attempt, while the same effect was not observed in males (Baud, Courtet, Perroud et al., 2007). We observed no sex difference in violence of method of attempt, nor did sex moderate the relationship between genotype and suicide attempt (data not shown) or genotype and aggressive/impulsive traits. Differences in diagnostic and gender composition of these studies make them difficult to compare, as does the use of different measures of anger, aggression, or hostility.

Lower serotonergic function has been consistently associated with suicide and suicide attempts (Mann & Currier, 2007), and low COMT activity may have a downstream developmental effect on 5-HIAA resulting in lower levels. There was a trend toward lower

CSF 5-HIAA in carriers of the Met Allele which is in a direction consistent with this relationship, however very wide confidence intervals (95% CI: -27.3, .769) indicate this finding is suggestive at best. Lower CSF 5-HIAA has been associated with greater aggression/impulsivity (Brown & Goodwin, 1986a; Stanley, Molcho, Stanley et al., 2000) and more highly lethal suicidal behavior (Åsberg, Thorén, Träskman et al., 1976; Mann, Currier, Stanley et al., 2006), and may be a pathway through which the functional variation of the COMT V158M is involved in suicidal behavior. However, we did not observe any direct effect of genotype on suicide attempt or indirectly via CSF 5-HIAA (data not shown).

Limitations

CSF monoamine data were available only for a modest sub-sample (although a larger sample than in most other studies) and so we may have lacked adequate statistical power to detect genotype effects. Ethnic stratification effect is always a concern in genetic association studies. We minimized this potential confound by including only Caucasians of European origins, however studies in other ethnic groups may yield different results.

Conclusions

We found no association of the COMT V158M with suicidal behavior or with clinical or putative biological endophenotypes for suicidal behavior in a large sample of Caucasian mood disorder subjects.

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COMT V158M Genotype Distribution by Diagnosis, Suicide Attempt Status, and Method and Lethality of Suicide Attempt in Mood Disorder Subjects

TABLE 1

Group (N)	Genotype distribution (%)						p ^b
	Genotypes			Met allele			
	Val/Val	Val/Met	Met/Met	p ^a	No Met allele	Met allele	
Controls (119)	27 (22.7)	67 (56.3)	25 (21)	.735	27 (22.7)	92 (77.3)	.440
Mood disorder (486)	127 (26.1)	264 (54.3)	95 (19.5)		127 (26.1)	359 (73.9)	
MDD (365)	94 (25.8)	202 (55.3)	69 (18.9)	.715	94 (25.8)	271 (74.2)	.742
Bipolar (212)	33 (27.3)	62 (51.2)	26 (21.5)		33 (27.3)	88 (72.7)	
Suicide attempt							
Yes (200)	34 (17)	114 (57)	53 (26)	.524	53 (26.5)	147 (73.5)	.916
No (180)	59 (21.1)	148 (52.9)	73 (26.1)		73 (26.1)	207 (73.9)	
Violent (28)	5 (18)	17 (61)	6 (21)	.623	5 (18)	23 (82)	.366
Non-violent (131)	34 (26)	75 (57)	22 (17)		34 (26)	97 (74)	
High lethality (69)	20 (29)	37 (53.6)	12 (17.4)	.455	20 (29)	49 (71)	.215
Low lethality (88)	18 (20.5)	54 (61.4)	16 (18.2)		18 (20.5)	70 (79.5)	

^a 2_{analysis} (df=2);

^b 2_{analysis} (df=1).

TABLE 2

Mood Disorder Subjects: GLM's for Clinical Rating Scale Scores and CSF Monoamine

	Model	COMT genotype
Impulsivity (BIS)	F = 3.76, df = 4, p = .005	F = .447, df = 2, p = .640 ^a
Hostility (BDH)	F = 4.81, df = 4, p = .001	F = 2.35, df = 2, p = .097 ^b
Aggression (BGHLA)	F = 4.79, df = 4, p = .001	F = .538, df = 2, p = .584 ^c
Current suicidal ideation *	F = 1.83, df = 4, p = .123	F = .999, df = 2, p = .369
CSF 5-HIAA †	F = 2.24, df = 4, p = .070	F = 1.74, df = 2, p = .180
CSF HVA †	F = 1.03, df = 4, p = .395	F = .945, df = 2, p = .392
CSF MHPG †	F = 1.36, df = 4, p = .254	F = 2.65, df = 2, p = .076

^a age 2 p<.001,^b age 2 p=.001,^c sex p=.026, age p<.001.

* Non-remitted Axis I patients only (N=358),

† N=111.