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COMT genotype and manic symptoms in schizophrenia

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Abstract

Inconsistencies in the relation between *COMT* variation and schizophrenia may be clarified by careful delineation of a target phenotype. The present study reports a significant association between a *COMT* haplotype and the severity of manic symptoms in 162 patients with schizophrenia or schizoaffective disorder (SZ). These data suggest that the effect of *COMT* variation may be associated with comorbid manic symptoms in SZ.

Keywords: COMT; Schizophrenia; Manic symptoms

1. Introduction

Catechol-*O*-methyltransferase (COMT) is an enzyme involved in the degradation of the neurotransmitter dopamine (DA). A single nucleotide polymorphism (SNP) within the human *COMT* gene ($Val_{158}Met$) dramatically affects the activity of the enzyme and as a result, directly influences DA availability in the brain (Harrison and Weinberger, 2005). Due to the long held belief that dysfunction within the DA system contributes to the pathogenesis of many psychiatric disorders, the functionality of *COMT* genetic variation has led to extensive investigation of this gene in psychiatric populations. To date, the strongest association of *COMT* genetic variation has been to schizophrenia but these findings have been inconsistent (Harrison and Weinberger, 2005).

Inconsistencies in the findings relating *COMT* variation to psychiatric disorders have been attributed to many factors. To date, most studies have focused on the $Val_{158}Met$ polymorphism and haplotypes containing this polymorphism. It is possible, however, that the *COMT* gene harbors more than one functional variant. For example, Handoko et al. (2004) reported that $Val_{158}Met$ confers risk for schizophrenia through its interactions with other functional SNPs within the *COMT* gene. It is also possible that a number of functional variants within the *COMT* gene collectively confer a generic risk for the development of psychiatric illness rather than increasing susceptibility to a specific psychiatric disorder. Recent findings by our group (Funke et al., 2005) support this suggestion and indicate that *COMT* variation is significantly associated with a

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broad "all affected" diagnostic group that includes a range of psychotic and affective disorders. In addition, associations have been reported between *COMT* and many psychiatric disorders including bipolar disorder, major depressive disorder, panic disorder, alcoholism, and obsessive–compulsive disorder (Smolka et al., 2005).

Based on recent data linking a *COMT* haplotype containing the valine allele of the Val_{158}Met polymorphism to both bipolar disorder and schizophrenia (Shifman et al., 2002, 2004), we suggest that the association between *COMT* genotype and illness may be refined by carefully delineating a target phenotype. For example, although patients with SZ often present with manic symptoms (Potash, 2006) most genetic studies do not report these comorbid features. It is possible, therefore, that prior reports of association between SZ and *COMT* are related to unspecified or unreported symptomatology within the cohort. Therefore, we tested for an association between *COMT* and manic symptoms in patients with schizophrenia or schizoaffective disorder. Specifically, we evaluated the relation between a 4-locus haplotype (comprised of −278 A/G, rs737865, Val_{158}Met and rs165599), which contains the Shifman et al. (2002, 2004) haplotype, and lifetime risk of manic symptoms in 162 subjects with schizophrenia or schizoaffective disorder.

2. Experimental/materials and methods

2.1. Subjects

The study sample was comprised of 162 (118 males, 44 females) Caucasian patients with a diagnosis of schizophrenia ($n=127$) or schizoaffective disorder ($n=35$) based on the Structured Clinical Interview for the DSM-IV (SCID). All subjects consented to a protocol approved by the Institutional Review Board of the North Shore-Long Island Jewish Health System (NSLIJHS). Subjects were recruited from inpatient and outpatient departments of the Zucker Hillside Hospital, a division of the NSLIJHS.

Each subject was assessed with an SCID administered by trained and reliable raters. The SCID contains a total of 7 items that assess lifetime history of manic symptoms including: elevated, euphoric or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech or talkativeness, flight of ideas or racing thoughts, distractibility, increase in activity and impulsivity. Ratings on each of the items were recorded based on the subject's report during the interview as well as the medical record and other available sources and are rated on a continuous scale where 1 = absent, 2 = subthreshold and 3 = present. These symptoms may be rated in the current mania section, the past mania section, or both of these sections in the SCID. For the present analysis, the highest mania rating, comprised of the sum of all 7 mania items in either the present or past mania section, was used as the dependent measure.

2.2. Analysis

Genotyping was conducted as previously described (Funke et al., 2005). The SNPHAP program (David Clayton, University of Cambridge, UK) was used for estimating haplotype frequencies.

A stepwise linear regression analysis including *COMT* haplotype and other variables that may influence the presentation of manic symptoms (sex, age, duration of illness, global assessment of functioning (GAF) score, severity of psychotic symptoms and premorbid IQ based on the Wide Range Achievement Test-Third Edition-Reading Subtest (WRAT-3) scores) was conducted to assess the effect of these variables on manic symptom severity.

3. Results

In the total sample of 162 subjects a single haplotype, AGGG, was identified that contained the 3-locus haplotype previously associated with schizophrenia and bipolar disorder (Shifman et al., 2002, 2004). Eleven homozygous carriers were identified but they did not differ from heterozygotes on any of our measures. Thus, homozygotes were grouped with the heterozygotes and all analyses were conducted between two groups: carriers ($n=63$) and non-carriers ($n=99$).

Comparison of the carriers to non-carriers revealed no significant differences in diagnostic status (65% schizophrenia vs. 59% schizoaffective disorder), sex (37.29% vs. 43.18% female; $\chi^2_{(df=1)}=0.47$, $p=0.49$), age (40.08, S.D. = 10.97 vs. 39.49, S.D. = 10.78; $t_{(df=160)}=0.33$, $p=0.74$), age of onset of illness (21.37, S.D. = 5.83 vs. 21.91, S.D. = 6.48; $t_{(df=160)}=-0.54$, $p=0.65$) or duration of illness (18.71, S.D. = 11.62 years vs. 17.59, S.D. = 10.19 years; $t_{(df=160)}=0.65$, $p=0.52$).

A stepwise multiple regression that included *COMT* haplotype, sex, age, duration of illness, GAF, severity of psychotic symptoms and WRAT-3 standard score revealed that *COMT* haplotype was the only significant predictor of the severity of manic symptoms ($F=5.31_{(df=1124)}$, $p=0.02$). Carriers of the risk haplotype had significantly higher mania ratings than non-carriers

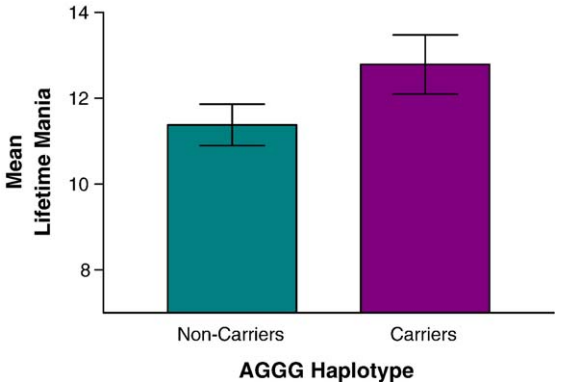

Fig. 1. Mean lifetime manic symptoms rating in non-carriers (11.48± 0.48) and carriers (12.79±0.69) of the *COMT* AGGG haplotype. Carrier status is shown on the *X*-axis. The *Y*-axis represents the mean lifetime mania ratings in carriers and non-carriers. (Error bars represent standard error of the mean.)

(Fig. 1) and genotype accounted for approximately 4% of the variance in the severity of manic symptoms.

4. Discussion

We detected a significant association between a *COMT* haplotype and lifetime severity of manic symptoms in a cohort of patients with schizophrenia and schizoaffective disorder. These results are consistent with previous studies that demonstrated an association between a 3-locus haplotype, subsumed by our current haplotype, and both schizophrenia and bipolar disorder.

Although catechol-*O*-methyltransferase is best characterized for its role in dopamine metabolism, it also plays a critical role in the degradation of norepinephrine (NE). Consistent with the noradrenergic model of mania, the relation between COMT and NE availability suggests that *COMT* may influence symptoms through the noradrenergic system. This hypothesis is supported by reports of aggression, mania and hypomania induced by norepinephrine reuptake inhibitors such as atomoxetine (Henderson and Hartman, 2004). Although the role of *COMT* genetic variation on norepinephrine metabolism is not known, a recent report has identified a role for the Val_{158}Met polymorphism in response to noradrenergic agents. Specifically, Szegedi et al. (2005) reported that patients with major depressive disorder that carry the valine allele respond better to treatment with mirtazapine, a tetracyclic antidepressant whose efficacy is thought to be associated with its effect on noradrenergic activity, than homozygous carriers of the methionine allele. This difference in treatment response based on *COMT* Val_{158}Met genotype was not observed for paroxetine, an SSRI with primarily serotonergic activity.

Several limitations of the current study should be noted. First, the SCID provides a comprehensive measure of the lifetime history of manic symptomatology, however, other assessment tools such as the Clinician-Administered Rating Scale for Mania or the Young Mania Rating Scale are more comprehensive. Second, we only analyzed a single *COMT* haplotype in our study. Although several other *COMT* haplotypes have been associated with schizophrenia, it was the only haplotype in our study that contained the 3-locus risk haplotype previously associated with both schizophrenia and bipolar disorder (Shifman et al., 2002, 2004). Nevertheless, other haplotypes, or functional alleles if detected, should be tested for association with clinical symptomatology in independent cohorts of subjects.

In conclusion, we have detected a significant association between a *COMT* haplotype and severity of manic symptoms in a relatively large cohort of patients with schizophrenia and schizoaffective disorder. These data suggest that *COMT* genotype may modify the clinical presentation of schizophrenia and provide further support for a molecular model of the classification of psychiatric illness.

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