Lack of Association of a Functional Catechol-O-Methyltransferase Gene Polymorphism in Schizophrenia

Rael D. Strous, Nigel Bark, Margaret Woerner, and Herbert M. Lachman

Key Words: Schizophrenia, polymorphism, catechol-O-methyltransferase, dopamine

Biol Psychiatry 1997;41:493–495

Introduction

Altered dopaminergic transmission is believed to play a role in the development of schizophrenia (Carlsson 1988). Consequently, a number of investigators have analyzed genes that encode dopamine receptor subtypes as potential candidates for schizophrenia susceptibility; however, genetic linkage analysis and association studies conducted on the dopamine transporter and dopamine receptor DRD1, DRD2, DRD3, DRD4, and DRD5 genes have been negative (Coon et al 1993; Campion et al 1994; Ravindranathan et al 1994; Macciardi et al 1995; Persico et al 1995; Sabate et al 1994; Sobell et al 1995).

Another gene that has the capacity to influence dopamine transmission is catechol-O-methyltransferase (COMT, enzyme code 2.1.1.6). COMT catalyzes the S-adenosyl-L-methionine dependent methyl conjugation of catecholamine neurotransmitters and catechol drugs (Axelrod and Tomchick 1958). COMT enzymatic activity in peripheral blood has previously been analyzed as a marker for schizophrenia, as well as for other psychiatric conditions; however, the results have been equivocal (Dunner et al 1977; Puzynski et al 1983; Philippu et al 1981; Karege et al 1987).

Renewed interest in COMT as a modifying gene in mental illness has been stimulated recently by observations made in velocardiofacial syndrome (VCFS), a congenital anomaly caused, in most cases, by a microdeletion on chromosome 22q11 (Shprintzen et al 1978; Scambler et al 1992; Driscoll et al 1993; Lindsay et al 1995; Morrow et al 1995). In addition to physical anomalies, an increased prevalence of psychiatric illness has also been observed, especially schizophrenia, attention-deficit hyperactivity disorder, and bipolar disorder (Shprintzen et al 1992; Chow et al 1994; Pulver et al 1994; Papalos et al 1996; Lachman et al 1996b). COMT maps to 22q11 and is deleted in most, if not all patients with deletional forms of VCFS (Grossman et al 1992; Scambler et al 1992).

COMT activity is governed by a common polymorphism that results in substantial three- to four-fold variations in enzymatic activity (Weinshilboum and Raymond 1977; Scanlon et al 1979; Aksoy et al 1993). We and others have recently shown that these functional differences are due to a valine → methionine substitution at codon 158 of the membrane-bound forms of COMT, which corresponds to codon 108 of the soluble or cytoplasmic form (Lotta et al 1995; Lachman et al 1996a). A valine at codon 108/158 results in the heat-stable, high-activity COMT variant, whereas a methionine at this position is found in the heat-labile, low-activity variant (Lachman et al 1996a).

The functional COMT polymorphism has now been analyzed in an association study conducted on patients diagnosed with schizophrenia.

Methods and Materials

Subjects

Chronic schizophrenics from Hillside Hospital–Long Island Jewish Medical Center (HILJ) and Bronx Psychiatric Center (BPC) participated in this study. All of the patients were
volunteers recruited through one of several research programs being conducted at the two institutions. Informed consent was provided prior to participation. Schizophrenia diagnoses at HHLLJ were based on a Schedule of Affective Disorders and Schizophrenia (SADS) interview using research diagnostic criteria (RDC) and DSM-III-R criteria. At BPC, a diagnosis of schizophrenia was made utilizing semistructured clinical interviews and chart review using DSM-III-R criteria. Forty-two Caucasian schizophrenics from HHLLJ and 12 from BPC were analyzed. The controls were 87 healthy Caucasian North American volunteers with no personal or family history of bipolar disorder or schizophrenia. Although no formal diagnostic assessments were conducted, the prevalence of schizophrenia in this selected group of volunteers would be expected to be less than 1%.

**Analysis of COMT Codon 108/158 Genotype**

The COMT genotype was determined by restriction fragment length polymorphism (RFLP) analysis as previously described in detail (Lachman et al 1996a). A 210 base pair polymerase chain reaction (PCR) product was generated using the primers 5'-CTCATCACCATCGAGATCAA and 5'-GATGACCCTGTGATAGTGG (nucleotides 1881-1900 and 2071-2090, GenBank accession number z26491; Bertocci et al 1991; Lundstrom et al 1991; Tenhunen et al 1994). The low-activity allele has an Nla III restriction site at codon 108/158 that can be identified by treating a radiolabeled PCR product (10 µL) with 5 units of Nla III, followed by resolution through an 8% nondenaturing acrylamide gel.

**Statistical Analysis**

Allele frequencies and genotypes were analyzed by chi-square using an Instat statistical program.

**Results and Discussion**

As seen in Table 1, the overall frequency of the low-activity COMT variant (met) and the number of patients homozygous for this allele are slightly increased compared with controls; however, the data do not reach statistical significance. The frequency of this allele in the control group is somewhat lower than that reported by Spielman and Weinshilboum (1981) and Daniels et al (1996) (.46 and .53, respectively). Using these historical values for the frequency of the COMT polymorphism in Caucasians, which in the Spielman and Weinshilboum study included nearly 900 North Americans, the results would be even less significant (not shown). These data suggest that the codon 108/158 polymorphism does not exert a major gene effect on the development of schizophrenia, in accordance with recent findings (Daniels et al 1996).

Association studies have been used for a number of years in complex inherited psychiatric disorders such as bipolar disorder and schizophrenia; however, the majority of these studies are limited by the use of polymorphic markers that, with few exceptions, are not functionally significant. In this association study, a functionally significant polymorphism that affects COMT enzymatic activity was analyzed. The logic of studying this polymorphism as a risk factor for neuropsychiatric disorders was strengthened by our recent finding that the low-activity form of COMT was associated with the development of rapid-cycling bipolar disorder occurring in a subgroup of psychiatrically affected patients with VCFS (Lachman et al 1996b); however, genotype and allele frequencies at COMT were not significantly different in schizophrenic patients from those found in controls. This negative finding does not rule the possibility that the COMT polymorphism may be a modifying factor in the development of a specific clinical subgroup of schizophrenia; however, substantial numbers of patients selected for specific phenotypes would be needed to determine if COMT, or any other candidate gene, can modify the core clinical features of schizophrenia.

**Table 1. COMT Polymorphism in Caucasian Schizophrenics**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Allele frequency</th>
<th>Genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>val</td>
<td>met</td>
</tr>
<tr>
<td>Controls (87)</td>
<td>.598</td>
<td>.402</td>
</tr>
<tr>
<td>Schizophrenia (54)</td>
<td>.481</td>
<td>.519</td>
</tr>
</tbody>
</table>

Allele frequency: χ² with Yates correction = 1 df, two tailed p = .07; genotype: χ² test of independence df = 2, p = .15. The genotype distributions are consistent with a Hardy-Weinberg equilibrium. val = high-activity allele; met = low-activity allele.

**References**


