Association Analysis of the Catechol *O*-Methyltransferase Gene and Bipolar Affective Disorder

Blanca Gutiérrez, B.Sc., Jaume Bertranpetit, Ph.D., Roser Guillamat, M.D., Vicenç Vallès, M.D., María J. Arranz, Ph.D., Robert Kerwin, Ph.D., M.D., and Lourdes Fañanás, Ph.D., M.D.

Objective: *Catechol* O*-methyltransferase (COMT) is an enzyme that inactivates catecholamines. Two common COMT alleles determine high and low activity of the enzyme. Previous studies using biochemical methods found lower enzyme activity in patients with major depression and bipolar disorder in comparison with control values, suggesting that a dysfunction in catecholamine metabolism may be related to the etiology of depression.* *Method:* *The authors studied two recently described DNA polymorphisms at the COMT gene (a silent C256G mutation and a structural mutation, Val-108-Met) in 88 patients with bipolar disorder and in 113 healthy comparison subjects, all of Spanish origin.* *Results:* *The frequency of the C256 allele was 0.58 in the patients and 0.54 in the comparison subjects. The frequency of the Val108 variant was 0.57 for both the patients and the comparison subjects. No allelic or genotypic associations were observed.* *Conclusions:* *The lack of association suggests that the COMT gene is not a major risk factor for bipolar disorder.*

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Bipolar affective disorder is a major mental disorder characterized by severe mood changes; it has a lifetime prevalence of 0.5%–1.5% (1). Genetic factors have long been implicated in the etiology of bipolar disorder, but little is known about the mode of inheritance, and many genes with small effects, as well as environmental factors, may be involved. Association analysis is one of the most powerful strategies—more so than linkage analysis—for detecting loci of small effects that cause susceptibility to disease (2).

Catechol *O*-methyltransferase (COMT) is an enzyme that inactivates catecholamines. There are two common variants of this enzyme. One presents a valine residue at position 108 of the protein (Val108) and the other has a methionine residue instead (Met108). The former shows high activity of the enzyme, and the latter (which is thermolabile at body temperature) presents low activity (3). Previous studies using biochemical methods have found different enzyme activity in patients with major depression and bipolar affective disorder than in control subjects (4, 5). In addition, several biochemical studies have found a relationship between high erythrocyte COMT activity and schizophrenia (6, 7). Thus, there is evidence suggesting that a dysfunction in catecholamine metabolism may be related to the etiology of these disorders. However, the interpretation of these studies is difficult because different and contradictory results have been detected, a variety of diagnostic schemes have been used, and COMT activity may be altered by antipsychotic drugs that act on the dopaminergic system. Recently, with the use of the transmission disequilibrium test, a genetic association between the low-activity allele and schizophrenia was found in a Chinese study group (8), although in a Caucasian study group there was no difference between schizophrenic patients and comparison subjects (9).

In the present study, we hypothesized that genetic variation in the COMT gene (mapped to chromosome 22q11 [10]) may have an effect in the etiology of bipolar affective disorder. We examined the DNA polymorphism described above (the coding mutation Val-108-Met) in subjects with bipolar affective disorder and in healthy comparison subjects. A second polymorphism,

Received March 11, 1996; revision received July 29, 1996; accepted Aug. 5, 1996. From Laboratori d'Antropologia, Facultat de Biologia, Universitat de Barcelona and Institut de Salut Pública de Catalunya, Barcelona; Departament de Psiquiatria, Consorci Hospitalari Parc Taulí, Sabadell, Barcelona; Departament de Psiquiatria, Hospital de Terrassa, Barcelona; and the Department of Psychological Medicine, Institute of Psychiatry, London. Address reprint requests to Dr. Fañanás, Laboratori d'Antropologia, Facultat de Biologia, Universitat de Barcelona, Diagonal 645, 08028 Barcelona, Spain.

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TABLE 1. Allele and Genotype Frequencies of the C256G and Val-108-Met Catechol *O*-Methyltransferase Polymorphisms in Patients With Bipolar Disorder and in Healthy Comparison Subjects

	Bipolar Patients[a]							
	Positive Family History[b] (N=56)		Negative Family History[c] (N=21)		Total Group (N=88)		Comparison Subjects (N=113)	
Variable	N	%	N	%	N	%	N	%
C256G polymorphism								
Genotype frequency								
C256/C256	19	34	6	29	28	32	33	29
C256/G256	26	46	12	57	46	52	56	50
G256/G256	11	20	3	14	14	16	24	21
Allele frequency								
C256	64	57	24	57	102	58	122	54
G256	48	43	18	43	74	42	104	46
Val-108-Met polymorphism								
Genotype frequency								
Val/Val	21	38	7	33	31	35	35	31
Val/Met	23	41	10	48	38	43	57	50
Met/Met	12	21	4	19	19	22	21	19
Allele frequency								
Val108	65	58	24	57	100	57	128	57
Met108	47	42	18	43	76	43	98	43

[a]Data on family history are missing for 11 of the 88 bipolar patients.
[b]Major affective disorder and/or schizophrenia in first-degree relatives.
[c]No major affective disorder or schizophrenia in first-degree relatives.

a silent C256G mutation (unpublished data), was also analyzed in the same study group. The C256G polymorphism has two genetic variants determined by a single exchange (one cytosine nucleotide for one guanine nucleotide) at position 256 of the COMT gene. The mutation at this point does not alter the final amino acid sequence of the protein. The goal of analyzing a silent genetic polymorphism was to be able to detect a possible linkage disequilibrium (nonrandom association of alleles at linked loci) between this marker and other genetic variants that may exist in the COMT gene. To our knowledge, no previous studies analyzing these polymorphisms in affective disorders, both bipolar and major depression, have been reported.

METHOD

The study group consisted of 88 hospital inpatients (37 men and 51 women) with severe bipolar affective disorder and 113 healthy comparison subjects (61 men and 52 women), all of Spanish origin. Patients and comparison subjects were matched to the same geographic area of Spain through the birthplaces of their grandparents. The patients had had an average of seven hospital admissions over 12 years since their first episode of illness. All patients strictly met the DSM-III-R criteria for bipolar disorder. The comparison subjects and their first-degree relatives had no evidence of psychiatric illness. A structured personal interview (11) was used with two healthy first-degree relatives of each proband in order to investigate the family history of psychiatric illness.

Written informed consent was obtained from both patients and comparison subjects after complete description of the study.

Genomic DNA was extracted from peripheral blood leukocytes with the use of a standard phenol-chloroform method. Two polymorphisms, a silent C256G mutation (described by David Collier, Department of Psychological Medicine, Institute of Psychiatry, London, personal communication) and a structural Val-108-Met change, were genotyped by means of a simple polymerase chain reaction amplification and two enzymatic digestions (method described elsewhere [9]).

The presence of an allelic or genotypic association was determined with the chi-square test of independence. The presence of the Hardy-Weinberg equilibrium was determined with the chi-square goodness-of-fit test. The power of the sample was calculated to determine the probability of detecting a statistically significant effect of a given magnitude. For the statistical analyses we used the EPI INFO statistical program (12).

RESULTS

For the C256G polymorphism, no significant differences in genotype frequencies were observed between the comparison subjects and the bipolar patients (table 1) (χ^2=0.93, df=2, p=0.63). Allele frequencies were also similar in the two groups (χ^2=0.63, df=1, p=0.43). Genotypes for both groups were in Hardy-Weinberg equilibrium. Frequencies of genotypes did not differ between groups when the bipolar patients were divided according to whether or not they had a family history of psychiatric illness (table 1). Furthermore, no differences between the sexes were found (for allele distribution, χ^2=3.01, df=1, p=0.08; for genotype distribution, χ^2=3.97, df=2, p=0.14).

For the Val-108-Met polymorphism, we found no differences between the patients and the comparison subjects in allele frequency (χ^2=0.00, df=1, p=0.94) or genotype frequency (χ^2=1.20, df=2, p=0.55). Both groups were in Hardy-Weinberg equilibrium. When the patients with a family history of psychiatric illness were compared with the healthy subjects, we did not find statistically significant differences in allele or genotype frequencies (table 1). Analysis of the data by sex showed similar distributions (for allele distribution, χ^2=1.96, df=1, p=0.16; for genotype distribution, χ^2=2.61, df=2, p=0.27).

DISCUSSION

Our results do not support the hypothesis that variation in the COMT gene may have a role in the development of bipolar affective disorder. The combined study group had more than 80% power to detect a mild allelic or genotypic association (odds ratio≥2.40) given the allele frequencies of the general population. We found no evidence of association with bipolar affective disorder or with any of the subgroups into which the study group was divided. However, since COMT is a major metabolizing enzyme of catecholamines that is

polymorphic for activity, it is likely to have some consequences for human behavior or disease. Although the present results make it unlikely that the COMT gene plays an important role in bipolar affective disorder, it is possible that it has a very small effect. In that case, a much larger study group would be required to establish whether such an association exists.

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