Brief Report

New Evidence of Association Between COMT Gene and Prefrontal Neurocognitive Function in Healthy Individuals From Sibling Pairs Discordant for Psychosis

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Objective: Using a sample of sibling pairs discordant for psychosis, the authors attempted to replicate the findings of previous studies suggesting that the functional genetic polymorphism *Val158Met* in the catechol *O*-methyltransferase (COMT) gene influences prefrontal cognitive function and increases the risk for schizophrenia.

Method: Eighty-nine sibling pairs discordant for psychosis were genotyped for this polymorphism and were assessed with the Wisconsin Card Sorting Test, a measure of prefrontal function. Additionally, the preferential transmission of alleles for this polymorphism was analyzed in a sample of 89 nuclear families in order to examine the genetic association.

Results: In the healthy siblings, a linear relationship was seen in which performance on the Wisconsin Card Sorting Test was associated in an allele dosage fashion with COMT genotype (i.e., fewer perseverative errors with higher number of methionine alleles). However, this association was not observed in patients. Furthermore, no evidence of genetic association with psychosis was detected.

Conclusions: These results seem to confirm the role of COMT genotype in the modulation of executive functions related to frontal lobe function in healthy individuals but not in schizophrenia patients.

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Schizophrenia is a complex disorder with a genetic contribution, variable psychopathological expression, and neurocognitive impairment. The view that dopamine plays a role in schizophrenia is long-standing, although the hypothesis of hyperdopaminergia to explain psychotic symptoms seems too simplistic (1).

Recently, electrophysiological, animal, and neuroimaging studies have pointed out that dopamine levels could enhance prefrontal cortex function (2). These data suggest that many of the cognitive impairments detected in schizophrenia patients could be related to reduced dopamine activity in this area.

The COMT gene codes for the enzyme catechol *O*-methyltransferase, which plays an important role in the degradative pathways of catecholaminergic neurotransmitters. The COMT gene, mapped to chromosome 22q11, contains a functional polymorphism (*Val158Met*) that consists of a transition at codon 158 of the gene that results in two common variants of the enzyme (*Val* and *Met*) corresponding to high and low activity, respectively (3).

It has been claimed that the variability of this gene could constitute a risk factor for schizophrenia. However, family-based association studies and case-control studies have produced a large but inconsistent bulk of results (4).

Egan and colleagues (5) examined the COMT *Val158Met* polymorphism in relation to brain physiology and cognitive function. They reported an association between the low-activity allele of the COMT gene (*Met*) and better performance on the Wisconsin Card Sorting Test (fewer number of perseverative errors) (6) in schizophrenia patients, their unaffected siblings, and healthy comparison subjects. According to these results, the high levels of dopamine in individuals with the *Met*/*Met* genotype enhance prefrontal function.

Recently, these results have been replicated in healthy individuals (7) and schizophrenia patients (8).

Our aims were 1) to investigate the association between COMT genotype and performance on the Wisconsin Card Sorting Test in a sample of sibling pairs discordant for schizophrenia spectrum disorders and 2) to explore the genetic association between the COMT gene and schizophrenia.

Method

The subjects participating in the study were 356 individuals from 89 nuclear families, which consisted of 89 patients affected by DSM-IV schizophrenia spectrum disorders and their fathers, mothers, and healthy siblings (sample described elsewhere [9]). Written informed consent was obtained from all participants.

The categorical breakdown of patient diagnoses was as follows: schizophrenia (53.9%, N=48), psychotic mood disorder (15.7%, N=14), schizoaffective disorder (12.4%, N=11), schizophreniform disorder (9%, N=8), brief psychotic disorder (5.6%, N=5), delusional disorder (2.2%, N=2), and atypical psychosis (1.1%, N=1). They were receiving antipsychotic drugs, mostly atypical antipsychotics (69.7%)

Schizophrenia patients and their healthy siblings were assessed with the Wisconsin Card Sorting Test. The number of per-

severative errors was the index used because it seems to best reflect prefrontal function. All patients were assessed after clinical stabilization.

COMT *Val158Met* genotypes were analyzed as described by Daniels and colleagues (10).

The effect of COMT genotype on Wisconsin Card Sorting Test performance was analyzed for each group separately (patients and healthy siblings) by using analysis of variance (ANOVA) and multiple regression. The multiple regression analysis was conducted to examine the association between the prefrontal function reflected in the Wisconsin Card Sorting Test and the number of *Met* alleles. All the associations were adjusted for possible confounding factors such as age, sex, and educational level.

The linkage of COMT alleles on risk to psychiatric phenotype was analyzed in a family-based association study using the transmission disequilibrium test (11).

Results

The genotype frequencies of the high-activity homozygote (*Val/Val*), heterozygote (*Val/Met*), and low-activity homozygote (*Met/Met*) in patients and in healthy siblings was not statistically different (χ^2=0.77, df=2, p=0.86). No significant differences were observed between the type of treatment that patients were receiving and COMT genotype (χ^2=2.1, df=2, p=0.30).

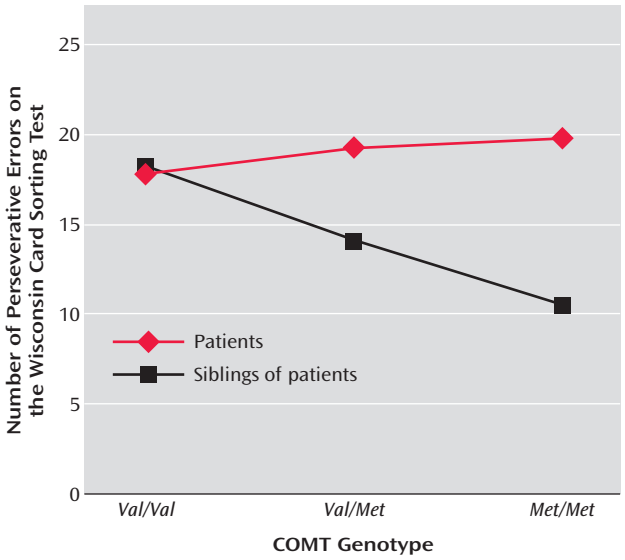
As expected, patients showed a higher number of perseverative errors on the Wisconsin Card Sorting Test compared with their unaffected siblings (t=3.2, df=88, p=0.001). No significant difference was found in perseverative errors on the Wisconsin Card Sorting Test between patients receiving atypical and typical antipsychotics (F=1.3, df=1, 84, p=0.30).

In the group of patients with psychosis, the ANOVA did not detect a significant effect of genotype on the number of perseverative errors (F=0.9, df=2, 84, p=0.40) (Figure 1). These findings remained essentially unchanged when the analysis was restricted to the subgroup of patients that met DSM-IV criteria for schizophrenia and schizoaffective disorder (N=67) (F=0.37, df=2, 63, p=0.70).

In the healthy siblings, individuals with the *Val/Val* genotype made more Wisconsin Card Sorting Test perseverative errors than those with other genotypes (F=5.5, df=2, 75, p=0.007) (Figure 1). Using multiple regression, the number of *Met* alleles was related to the number of perseverative errors (β=4.4, p=0.005). Furthermore, there was evidence of monotonic linear decrease in the number of perseverative errors with higher number of Methionine alleles (β_{0Met}=8.4, β_{1Met}=3.2, β_{2Met}=1.0).

In the 89 families, the transmission disequilibrium test did not show a preferential transmission of alleles from the heterozygous parents to the affected and nonaffected siblings (allele-wise transmission disequilibrium test for patients: χ^2=1.5, p=0.20; allele-wise transmission disequilibrium test for healthy siblings: χ^2=0.5, p=0.40).

FIGURE 1. Effect of COMT Genotype on Wisconsin Card Sorting Test Performance in Sibling Pairs (N=89) Discordant for Psychosis



Discussion

Our results do not seem to support the role of the *Val158Met* polymorphism in the risk for schizophrenia spectrum disorders.

Concerning the analysis of the association between performance on the Wisconsin Card Sorting Test and the functional polymorphism *Val158Met* in the COMT gene, our results confirm an effect of COMT *Val158Met* genotype on prefrontal cortical function in healthy siblings. These findings are consistent with previous studies conducted in healthy individuals (5, 7). The strong association between the COMT genotype and the neuropsychological test of executive function (Wisconsin Card Sorting Test) was detected in an allele dosage fashion. This linear trend is consistent with the fact that heterozygous individuals (*Val/Met*) have an enzyme activity that is midway between homozygote (*Val/Val*) individuals, who display high COMT activity, and *Met/Met* individuals, who have four to five times lower COMT activity (3). However, in the group of patients we failed to find an association between COMT genotype and perseverative errors on the Wisconsin Card Sorting Test, unlike previous studies (6, 8). One possible explanation could be that other dopaminergic alterations could mask the COMT effect that we have studied. Several lines of evidence suggest that dopamine innervation of the prefrontal cortex may be abnormal in psychosis (12). In this sense, a decreased density/hyposensitivity or blockage of some dopamine receptors in the prefrontal cortex could also be responsible for the deficits in the cognitive tasks.

A possible confounding factor in the interpretation of these results is the heterogeneity of diagnoses in our sample, which included several schizophrenia spectrum disorders. However, the analyses with a more homogenous

sample of patients (schizophrenia and schizoaffective diagnosis) revealed the same pattern described in the larger sample of patients.

On the other hand, according to our analyses, the lack of association is unlikely to be due to the type of medication that patients received.

Further studies are necessary in order to clarify the specific risk of this polymorphism in the etiology or pathophysiology of schizophrenia and in the cognitive deficits described in these patients.

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References

1. Carlsson A: The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1988; 1:179–186
2. Braver TS, Barch DM, Cohen JD: Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. Biol Psychiatry 1999; 46:312–328
3. Lachman HM, Morrow B, Shprintzen R, Veit S, Parsia SS, Faedda G, Goldberg R, Kucherlapati R, Papolos DF: Association of codon 108/158 catechol-O-methyltransferase gene polymorphism with the psychiatric manifestations of velo-cardiofacial syndrome. Am J Med Genet 1996; 67:468–472
4. Glatt SJ, Faraone SV, Tsuang MT: Association between a functional catechol *O*-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. Am J Psychiatry 2003; 160:469–476
5. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR: Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA 2001; 98:6917–6922
6. Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G: Wisconsin Card Sorting Test Manual. Odessa, Fla, Psychological Assessment Resources, 1993
7. Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D: A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry 2002; 159:652–654
8. Joober R, Gauthier J, Lal S, Bloom D, Lalonde P, Rouleau G, Benkelfat C, Labelle A: Catechol-O-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test (letter). Arch Gen Psychiatry 2002; 59:662–663
9. Rosa A, Peralta V, Papiol S, Cuesta MJ, Serrano F, Martínez-Larrea A, Fañanás L: Interleukin-1beta (IL-1beta) gene and increased risk for the depressive symptom-dimension in schizophrenia spectrum disorders. Am J Med Genet 2004; 124B:10–14
10. Daniels JK, Williams NM, Williams J, Jones LA, Cardno AG, Murphy KC, Spurlock G, Riley B, Scambler P, Asherson P, McGuffin P, Owen MJ: No evidence for allelic association between schizophrenia and a polymorphism determining high or low catechol *O*-methyltransferase activity. Am J Psychiatry 1996; 153:268–270
11. Spielman RS, McGinnis RE, Ewens WJ: Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). Am J Hum Genet 1993; 52:506–516
12. Meador-Woodruff JH, Haroutunian V, Powchik P, Davidson M, Davis KL, Watson SJ: Dopamine receptor transcript expression in striatum and prefrontal and occipital cortex: focal abnormalities in orbitofrontal cortex in schizophrenia. Arch Gen Psychiatry 1997; 54:1089–1095