Catechol-*O*-methyltransferase gene polymorphisms in Saudi cases with schizophrenia

Ashraf Tantawy[a,b], Abduhamid Al-Yahia[c], Yasser Raya[c,d], Abdurrahman Al-Mohaimeed[e], Ahmad Settin[f]

[a]Department of Psychiatry, Faculty of Medicine, Suez Canal University, Ismailia, Egypt, [b]Buraidah Mental Hospital, Al-Qassim, [c]Psychiatry, College of Medicine, Qassim University, Al-Qassim, Kingdom of Saudi Arabia, [d]Department of Psychiatry, Faculty of Medicine, Zagazig University, Zagazig, Egypt, [e]Family and Community Medicine, [f]Departments of Paediatrics, College of Medicine, Qassim University, Al-Qassim, Kingdom of Saudi Arabia

Correspondence to Ashraf Tantawy, MD, Department of Psychiatry, Faculty of Medicine, Suez Canal University, Ismailia, Egypt
Tel: 01146298057; fax: 064/3208542;
E-mail: tantawy99@hotmail.com

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Background
This work was conducted to test for the association of genetic polymorphisms of catechol-*O*-methyltransferase (*COMT*) with the susceptibility and clinical patterns of schizophrenia among Saudi patients.

Participants and methods
This is a case–control study involving 79 patients fulfilling the ICD-10 criteria of schizophrenia and 82 healthy controls. Patients were interviewed by different tools, which included the Diagnostic Interview for Genetic Studies (DIGS/V4.0), the Positive and Negative Symptoms Scale (PANSS), and the World Health Organization Disability Assessment Schedule (version 2.0) (WHO/DAS II). All patients and controls were screened for *COMT G >A* gene polymorphisms using the real-time PCR technique.

Results
Frequencies of all genetic variants of *COMT G >A* [*V158M*] did not show a significant difference on comparing cases with controls ($P > 0.05$). Comparing the frequencies of genetic variants in cases having positive parental consanguinity and a family history of schizophrenia or other mental illnesses with those without a history also showed nonsignificant results ($P > 0.05$). A stratified analysis related to severity scores and associated clinical illnesses also showed a nonsignificant difference ($P > 0.05$).

Conclusion
Polymorphism related to *COMT* G >A was not associated with the susceptibility and the severity of schizophrenia among Saudi cases.

Keywords:
catechol-*O*-methyltransferase, gene polymorphism, Saudi Arabia, schizophrenia

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Introduction

Schizophrenia is a psychiatric disorder that affects ~1% of the world population, usually begins before 25 years of age and persists throughout life, and affects persons of all social classes (McGuffin *et al.*, 1995; APA, 2000). Schizophrenia, like most psychiatric disorders, is a complex disorder that cannot be explained by a single genetic or environmental factor (McGuffin *et al.*, 1995). The heritability of schizophrenia is estimated to be around 80%, with around a 10-fold risk increase in first-degree relatives (Owen *et al.*, 2005). Association studies, mainly with candidate genes, have also not provided consistent results (Pulver, 2000; Shifman *et al.*, 2002; Glatt *et al.*, 2003; Wonodi *et al.*, 2003).

Catechol-*O*-methyltransferase (*COMT*) is one of the enzymes that degrade catecholamines, including dopamine (Axelrod and Tomchick, 1958; Grossman *et al.*, 1992; Slifstein *et al.*, 2008).Two codominant alleles (G and A) in exon 4 of the *COMT* gene influence the amino acid structure (Val or Met) at codon 158. The *COMT* enzyme activity is genetically polymorphic, with a trimodal distribution (high activity in the Val/Val genotype, intermediate activity in the Val/Met genotype, and low activity in the Met/Met genotype) (Grossman *et al.*, 1992). Results of the studies on the Val158Met polymorphism of the *COMT* gene are conflicting (Lachman *et al.*, 1996; Shifman *et al.*, 2002; Glatt *et al.*, 2003; Wonodi *et al.*, 2003; Chen *et al.*, 2004a, 2004b), with a number of studies suggesting a possible effect of the Val158Met polymorphism on the vulnerability to schizophrenia (Kunugi *et al.*, 1997; Ohmori *et al.*, 1998; Egan *et al.*, 2001; Liou *et al.*, 2001; Weinberger *et al.*, 2001; Shifman *et al.*, 2002; Kremer *et al.*, 2003; Wonodi *et al.*, 2003; Bertolino *et al.*, 2004; Chen *et al.*, 2004a, 2004b; Sazci *et al.*, 2004; Meyer-Lindenberg *et al.*, 2006; Nunokawa *et al.*, 2007; Park *et al.*, 2009; Hoenicka *et al.*, 2010; Costas *et al.*, 2011), and others showing no association or are not specific to schizophrenia (Daniels *et al.*, 1996; Strous *et al.*, 1997; Karayiorgou *et al.*, 1998; Chen *et al.*, 1999; Norton *et al.*, 2002; Glatt *et al.*, 2003; Inada *et al.*, 2003; Mattay *et al.*, 2003; Palmatier *et al.*, 2004; Fan *et al.*, 2005; Galderisi *et al.*, 2005; Munafo *et al.*, 2005;

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Williams *et al.*, 2005; Barnett *et al.*, 2007; Gur *et al.*, 2007; Kim *et al.*, 2008; Okochi *et al.*, 2009; Park *et al.*, 2009; Nieratschker *et al.*, 2010; Lajin *et al.*, 2011). Although the effect of the *COMT* gene on the deficit (negative symptoms)/nondeficit (positive symptoms) subtype of schizophrenia has failed to be shown (Fan *et al.*, 2005; Williams *et al.*, 2005; Wonodi *et al.*, 2006; Fanous and Kendler, 2008), some studies found an association between the *COMT* gene and the severity of positive symptoms: aggressive or violent behavior in schizophrenic individuals (Roffman *et al.*, 2006; Hill *et al.*, 2011). Several aspects of *COMT* function, including its transcription and its inactivation of dopamine by transmethylation, depend on the availability of one-carbon moieties, which in turn is strongly influenced by the activity of methylenetetrahydrofolate reductase (*MTHFR*) (Sasaki *et al.*, 2003). Therefore, it was suggested that the *MTHFR* 677C >T genotype disrupts prefrontal function in schizophrenia through an interaction with *COMT* 158Val >Met (Kang *et al.*, 2010).

This work was conducted to check for the association of polymorphic variants of *COMT* A >G [Val158Met] with the susceptibility and the clinical pattern of schizophrenia among Saudi individuals.

Participants and methods

This was a randomized case–control study involving 79 patients with schizophrenia and 82 healthy unrelated controls. Cases were selected randomly from the mental health hospital in Al-Qassim region, Saudi Arabia. They included 57 (72.2%) male and 22 (27.8%) female patients. Their mean ± SD age of onset of the disease was 24.3±7.6 years. Diagnostic tools were based on a semistructured psychiatric interview involving the Diagnostic Interview for Genetic Studies Version 4.0 (DIGS/V4.0) (Bierut *et al.*, 2005) in addition to the International Classification of Mental and Behavioral Disorders (ICD-10) (WHO, 1994). Exclusion criteria included cases with mental retardation, chronic debilitating illness, organic brain disease, substance abuse disorder, or psychiatric comorbidities. Controls were selected from blood donors who were absolutely free of and had a negative family history of any psychiatric illness. They included 49 (56.1%) male and 36 (43.9%) female individuals with a mean age ± SD of 27.2 ± 11.1 years. An ethical approval was taken from all participants before the start of the study, and approval from the Research and Ethical committees of Al-Qassim University, Saudi Arabia, was obtained.

Measurement of disability and the severity

The severity of schizophrenia was assessed by the application of the commonly used rating scale: the Positive and Negative Symptoms Scale (PANSS) for schizophrenia. To assess a patient using PANSS, an ~45-min clinical interview is conducted. The patient is rated from 1 to 7 (1 =absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate severe, 6 = severe, and 7 = extreme) on 30 different symptoms on the basis of the interview as well as reports of family members or primary-care hospital workers (Annicchiarico, 2003). In contrast, disability was measured with the World Health Organization Disability Assessment Schedule (version 2.0) (WHO/DAS II). This interview measures the self-reported difficulty of functioning in six major domains that are considered important in most cultures: D1, understanding and communicating; D2, getting around; D3, self-care; D4, getting along with people; D5, life activities; and D6, participation in the society (Kay *et al.*, 1987).

DNA extraction and real-time PCR

The isolation of DNA was performed on a MagNA Pure LC instrument (Roche Molecular Biochemicals, Mannheim, Germany). Real-time PCR was performed using the light cycler instrument (Roche Diagnostics, Mannheim, Germany). Oligonucleotide primers and fluorescence-labeled hybridization probes were designed for amplification and sequence-specific detection of *COMT* gene polymorphisms. Primers and probes were obtained from TIB MolBiol (Berlin, Germany). The master mixture contained 2 μl of a 10× mixture of LightCycler FastStart DNA master hybridization probes (Roche Diagnostics), 5 mmol/l $MgCl_2$ (final concentration), a 1 μmol/l final concentration of primers, and a 0.2 μmol/l final concentration of hybridization probes. Fluorescence curves were analyzed with the Light Cycler software (version 3.5.3). Each run contained the wild type, the mutant, and heterozygous standard control DNA in addition to a negative control (blank reagent and water). Each result was confirmed by the specific peak in the corresponding melting curve.

Statistical analysis

Data were processed and analyzed using the Statistical Package of Social Science (SPSS, version 13.0, SAS Institute, Cary, NC, USA). The frequency of the studied genotypic and allelic polymorphisms among cases was compared with that of controls and tested for a positive association using the χ^2-test, Fisher's exact test, and odds ratio with the 95%

confidence interval considering a minimum level of significance of *P* value less than 0.05 (SPSS, 2002).

Results

The frequency of genetic variants related to *COMT G >A* [*V158M*] polymorphisms among schizophrenic patients compared with controls showed no statistically significant difference with regard to different models of inheritance such as the recessive (homozygosity of the rare allele vs. others), the codominant (homozygosity or heterozygosity of the rare allele vs. homozygosity of the wild-type allele), and the overdominant (heterozygosity vs. others) patterns (Table 1). The Hardy–Weinberg equilibrium also showed no significant deviation of the observed frequencies from that of the expected frequencies, among both cases and controls, indicating a fairly selected population sample with no particular differences of cases and controls.

Evaluation of the subtypes of schizophrenic patients revealed that among them, undifferentiated schizophrenia was the most common subtype (31, 39.24%), followed by the paranoid (25, 31.65%), the residual (18, 22.78%), and the hebephrenic (5, 6.33%) subtypes. Genetic predisposition of the disease was shown by the fact that 21 (26.58%) cases had a positive family history of schizophrenia, whereas 18 (22.78%) cases had a family history of other mental disorders, and only seven (8.86%) cases had positive parental consanguinity. Hypertension and diabetes were found among 12 (15.19%) and 16 (20.25%) cases, respectively. Comparing genetic variants in subgroups of cases regarding their sex, a positive family history of schizophrenia or other mental disorders, consanguinity, and any associated medical conditions such as diabetes, hypertension, and metabolic syndrome also showed a nonsignificant difference (Tables 2 and 3). Evaluation of severity and disability scores through the calculation of their mean ± SD related to their individual genetic background showed a nonsignificant difference (Table 4).

Discussion

This study was conducted to check for the association of genetic polymorphisms of the *COMT* gene with schizophrenia among affected cases in Saudi Arabia. Although a number of studies including a meta-analysis have suggested an association between schizophrenia and the *COMT* polymorphism in several populations (Kunugi *et al.*, 1997; Ohmori *et al.*, 1998; Egan *et al.*, 2001; Liou *et al.*, 2001; Weinberger *et al.*, 2001; Shifman *et al.*, 2002; Kremer *et al.*, 2003; Wonodi *et al.*, 2003; Bertolino *et al.*, 2004; Chen *et al.*, 2004a, 2004b; Sazci *et al.*, 2004; Meyer-Lindenberg *et al.*, 2006; Nunokawa *et al.*, 2007; Allen *et al.*, 2008; Park *et al.*, 2009; Hoenicka *et al.*, 2010; Costas *et al.*, 2011), this study failed to demonstrate any significant association between these polymorphisms and the susceptibility to schizophrenia among Saudi individuals. Nonetheless, this negative association was also reported in other studies and meta-analyses among several other populations (Daniels *et al.*, 1996; Strous *et al.*, 1997; Karayiorgou *et al.*, 1998; Chen *et al.*, 1999; Norton *et al.*, 2002; Glatt *et al.*, 2003; Inada *et al.*, 2003; Mattay *et al.*, 2003; Palmatier *et al.*, 2004; Fan *et al.*, 2005; Galderisi *et al.*, 2005; Munafo *et al.*, 2005; Williams *et al.*, 2005; Barnett *et al.*, 2007; Gur *et al.*, 2007; Kim *et al.*, 2008; Okochi *et al.*, 2009; Park *et al.*, 2009; Kang *et al.*, 2010; Nieratschker *et al.*, 2010; Lajin *et al.*, 2011). Such inconsistent and controversial results might be confirmatory of the complex nature of the disease, presumably having a polygenic or a multifactorial basis. It might also be explained by the ethnic diversity and differing environmental factors. Technical errors might also warrant further research work with more precise methodologies and larger population samples. Schizophrenia among the Saudi cases of this study had some issues pointing toward its genetic background, such as a positive family history of schizophrenia among more than one-fourth of the cases, a positive family history of mental disorders among more than one-fifth of them, and positive parental consanguinity in ~9% of them. However, these subgroups did not show an association with the

Table 1 Gene polymorphic variants related to *COMT G >A [V158M]* among cases of schizophrenia compared with controls

Gene Polymorphic Variants	Cases [*N* (%)]	Controls [*N* (%)]
Total	76 (100.0)	82 (100.0)
COMT G >A [*V158M*]		
GG (*158 V/V*)	22 (28.9)	22 (27.5)
GA (*158 V/M*)	33 (43.4)	36 (45.0)
AA (*158 M/M*)	21 (27.6)	22 (27.5)
Recessive (AA vs. GG + GA)	$P = 1.0$	OR (95% CI) = 0.99 (0.5–1.99)
Codominant (AA vs. GG)	$P = 0.92$	OR (95% CI) = 0.95 (0.4–2.2)
Codominant (GA vs. GG)	$P = 0.97$	OR (95% CI) = 0.92 (0.4–2.0)
Overdominant (GA vs. GG + AA)	$P = 0.5$	OR (95% CI) = 0.8 (0.4–1.4)
HWE	$\chi^2 = 1.3$, $P > 0.05$	$\chi^2 = 0.8$, $P > 0.05$

CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio.

Table 2 Gene polymorphic variants related to *COMT* G >A [V158M] among cases of schizophrenia in relation to their demographic parameters

COMT G >A [V158M]	GG [*N* (%)]	GA [*N* (%)]	AA [*N* (%)]
Sex			
Males	16 (29.1)	24 (43.6)	15 (27.3)
Females	6 (28.6)	9 (42.9)	6 (28.6)
P	0.9		
Consanguinity			
Negative	20 (29.0)	31 (44.9)	18 (26.1)
Positive	2 (28.6)	2 (28.6)	3 (42.9)
P	0.6		
Family history of schizophrenia			
Negative	18 (32.1)	23 (41.1)	15 (26.8)
Positive	4 (20.0)	10 (50.0)	6 (30.0)
P	0.6		
Family history of mental illness			
Negative	19 (32.2)	26 (44.1)	14 (23.7)
Positive	3 (17.6)	7 (41.2)	7 (41.2)
P	0.3		

Table 3 Gene polymorphic variants related to *COMT* G >A [V158M] among cases of schizophrenia in relation to their clinical parameters

COMT G >A [V158M]	GG [*N* (%)]	GA [*N* (%)]	AA [*N* (%)]
Subtypes			
Paranoid	7 (30.4)	9 (39.1)	7 (30.4)
Hebephrenic	2 (40.0)	3 (60.0)	00.0
Residual	6 (26.1)	12 (52.2)	5 (21.7)
Undifferentiated	9 (30.0)	12 (40.0)	9 (30.0)
P	0.9		
Diabetes			
Negative	17 (28.3)	24 (40.0)	19 (31.7)
Positive	5 (31.3)	9 (56.3)	2 (12.5)
P	0.3		
Hypertension			
Negative	19 (29.7)	27 (42.2)	18 (28.1)
Positive	3 (25.0)	6 (50.0)	3 (25.0)
P	0.9		
Metabolic syndrome			
Negative	21 (29.6)	32 (45.1)	18 (25.4)
Positive	1 (20.0)	1 (20.0)	3 (60.0)
P	0.2		

Table 4 Gene polymorphic variants related to *COMT* among schizophrenic patients in relation to severity of illness and disability scores

Scores (mean ± SD)	COMT G >A [V158M]		
	GG	GA	AA
PANSS P	3.73 ± 1.35	3.67 ± 1.49	3.67 ± 1.35
P (*t*-test)	Reference	>0.05	>0.05
PANSS N	3.73 ± 1.55	3.61 ± 1.73	3.38 ± 1.40
P (*t*-test)	Reference	>0.05	>0.05
PANSS GP	3.95 ± 1.33	4.58 ± 1.20	4.29 ± 1.10
P (*t*-test)	Reference	>0.05	>0.05
DAS-II D1	3.18 ± 0.73	3.18 ± 0.81	3.14 ± 0.73
P (*t*-test)	Reference	>0.05	>0.05
DAS-II D2	3.00 ± 0.62	3.21 ± 0.65	3.24 ± 0.77
P (*t*-test)	Reference	>0.05	>0.05
DAS-II D3	3.27 ± 0.88	3.18 ± 0.88	3.29 ± 0.90
P (*t*-test)	Reference	>0.05	>0.05
DAS-II D4	3.36 ± 0.66	3.42 ± 0.75	3.38 ± 1.02
P (*t*-test)	Reference	>0.05	>0.05
DAS-II D5	3.27 ± 0.70	3.48 ± 0.62	3.38 ± 0.87
P (*t*-test)	Reference	>0.05	>0.05
DAS-II D6	3.32 ± 0.78	3.42 ± 0.83	3.33 ± 0.97
P (*t*-test)	Reference	>0.05	>0.05

D1, understanding and communicating; D2, getting around; D3, self-care; D4, getting along with people; D5, life activities; D6, participation in the society; DAS-II, Disability Assessment Schedule V2; PANSS GP, Positive and Negative Symptoms Scale General Psychopathology Score; PANSS N, Positive and Negative Symptoms Scale Negative Score; PANSS P, Positive and Negative Symptoms Scale Positive Score.

genetic variants of the *COMT* gene. Also, these genetic variants were not associated with schizophrenia subtypes or with other clinical disorders such as diabetes and hypertension. These results are consistent with prior reports on the negative genetic association with the subtypes of schizophrenia (Fan *et al.*, 2005; Williams *et al.*, 2005; Fanous and Kendler, 2008; Hill *et al.*, 2011), although some linkage and association studies have suggested that some susceptibility genes are etiologic factors for more or less specific subtypes of schizophrenia (Karayiorgou *et al.*, 1998; Chen *et al.*, 1999; Kirkpatrick *et al.*, 2001). This study also showed a negative association for positive and negative disease manifestations. These results are inconsistent with some other studies that showed some association (Weinberger *et al.*, 2001; Bilder *et al.*, 2004; Levy and Dubois, 2006; Roffman *et al.*, 2006; Wonodi *et al.*, 2006; Fanous and Kendler, 2008; Gu *et al.*, 2009; Pan *et al.*, 2009; Hill *et al.*, 2011; Ceaser *et al.*, 2012) and also are in agreement with other studies that failed to show any association (Fan *et al.*, 2005; Williams *et al.*, 2005; Wonodi *et al.*, 2006; Fanous and Kendler, 2008; Maher, 2008). It was previously proven through a meta-analysis and an association study that there is no direct relationship between *COMT* and suicidal behavior (Calati *et al.*, 2011; Soyka, 2011). These finding are inconsistent with most of the previous studies (Green, 1996; Egan *et al.*, 2001; Bertolino *et al.*, 2004; Meyer-Lindenberg *et al.*, 2006; Gur *et al.*, 2007; Ceaser *et al.*, 2012). The majority of the individuals with schizophrenia were treated with antipsychotic medication and most of these individuals were treated with atypical drugs. The medication status could have interacted with the influences of *COMT* genotypes in our study, but *COMT* effects have previously been observed in nontreated patients (Woodward *et al.*, 2007). The difference can be explained by the relatively small sample size, which might have limited the detection of associations between the *COMT* gene and subtypes

of schizophrenia. We conclude that polymorphisms related to *COMT G >A* were not associated with the susceptibility to schizophrenia among Saudi cases.

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Conflict of interest

There are no conflicts of interest.

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