



Genetic association of catechol-O-methyltransferase val(158)met polymorphism in Saudi schizophrenia patients

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ABSTRACT. Schizophrenia is a complex neuropsychiatric disorder strongly associated with dopamine dysregulation. Catechol-O-methyltransferase (COMT) is a candidate gene for schizophrenia that encodes an enzyme involved in the metabolic inactivation of dopamine. The COMT Val¹⁵⁸Met polymorphism has been associated with schizophrenia and has significant inter- and intra-ethnic variations. We examined a possible association between the COMT Val¹⁵⁸Met polymorphism and schizophrenia in Saudis, taking into account gender and functional symptoms. Saudi subjects including 172 unrelated schizophrenia patients and 177 matched controls were analyzed for allele and genotype distribution of the COMT Val¹⁵⁸Met polymorphism. We found significant differences in allele and genotype frequencies between patients and controls. The frequencies of Met¹⁵⁸ allele (A) and genotype Val¹⁵⁸Met (GA) were significantly higher in patients compared to those in controls. On the other hand, the frequencies of Val¹⁵⁸ allele (G) and genotype Val¹⁵⁸Val (GG) were significantly higher in controls than those in patients. We found a significant association of the COMT Val¹⁵⁸Met

polymorphism with schizophrenia. Moreover, male patients with the COMT Val¹⁵⁸Met polymorphism had increased risk for schizophrenia compared to female subjects. However, no association was noticed with the COMT Val¹⁵⁸Met polymorphism and negative or positive symptoms of schizophrenia. These results provide evidence for a role of the COMT Val¹⁵⁸Met polymorphism in the etiopathophysiology of schizophrenia in Saudi population. It appears that the association of the COMT Val¹⁵⁸Met polymorphism with schizophrenia is mediated by gender.

Key words: Schizophrenia; Catechol-O-methyltransferase (COMT); Polymorphism

INTRODUCTION

Schizophrenia is one of the most disabling psychiatric disorders, which according to the World Health Organization affects around 24 million people worldwide, with a prevalence ranging from 0.7 to 1.1%. Schizophrenia affects men and women equally, but its onset in women is typically 5 years later than in men. On the other hand, schizophrenia has long been regarded as a heterogeneous entity, and over the decades researchers have sought consistent subpatterns that could explain different aspects of this complex disorder. Andreasen and Olsen (1982) have proposed that two distinct syndromes in schizophrenia can be discerned from the phenomenal profiles. Type I, or positive syndrome is composed of florid symptoms such as delusions, hallucinations and disorganized thinking, which are superimposed on the mental status. Type II, or negative syndrome is characterized by deficits in cognitive, affective and social functions, including blunting of affect and passive withdrawal (Kay et al., 1987). It has been speculated that these syndromes in schizophrenia bear etiological, pharmacological and prognostic import. Due to its early age of onset and the lifelong disability generally accompanied by emotional and financial devastation, schizophrenia brings to its victims and their families, it is one of the most catastrophic mental illnesses. Available data suggest that the etiology of schizophrenia involves the interplay of complex polygenic influences and environmental risk factors operating on brain maturational processes. Numerous studies have shown that schizophrenia is a multifactorial disease involving several genes, with each susceptibility gene having only a modest individual effect (Harrison and Weinberger, 2005).

Dopamine dysregulation has long been believed to be associated with schizophrenia pathogenesis (Howes et al., 2009). Catechol-O-methyltransferase (COMT) [MIM 116790] is a catabolic enzyme involved in the degradation of a number of bioactive molecules including dopamine. The enzyme is encoded by the COMT gene. COMT is located (along with 47 other genes) in a fragment of chromosome 22q11 that when deleted results in a complex syndrome, the psychiatric manifestations of which include schizophrenia and other psychoses (Murphy, 2002). These observations have placed COMT near the top of a rather long list of plausible candidate genes for schizophrenia. The ability to test the hypothesis that COMT may be a susceptibility gene for schizophrenia has been simplified in principle by the existence of a valine-to-methionine (Val¹⁵⁸Met) polymorphism (rs4680), which results respectively in high- and low-activity forms of the enzyme (Lotta et al., 1995). Given the unequivocal effect of this polymorphism on the function of COMT, and the evidence for a critical role for dopamine in the pathophysiology and treatment of psychosis, there are strong prior expectations that

Val¹⁵⁸Met influences susceptibility to schizophrenia as well as other psychiatric phenotypes. Indeed, the Val¹⁵⁸Met polymorphism has become the most widely studied polymorphism for various psychiatric diseases including schizophrenia. Several investigators have reported a significant association between the COMT polymorphism and schizophrenia (Sazci et al., 2004; Lafuente et al., 2008; Gupta et al., 2009; Hoenicka et al., 2010; Costas et al., 2011; Wan et al., 2011), while other studies have shown a lack of association between the COMT (Val¹⁵⁸Met) polymorphism and schizophrenia (Karayiorgou et al., 1998; Okochi et al., 2009; Kong et al., 2011; Zhang et al., 2012). Moreover, the results of the studies on Caucasian and Asian ethnic groups have shown both inter- and intra-ethnic variations (Rosa et al., 2004; Gupta et al., 2009; Nieratschker et al., 2010; Wang et al., 2010). Since the findings of previous studies on the role of COMT (Val¹⁵⁸Met) polymorphism in schizophrenia remain inconclusive, this study was undertaken to determine the association between the COMT (Val¹⁵⁸Met) polymorphism and schizophrenia with emphasis on the role of gender and functional symptoms in Saudi patients.

MATERIAL AND METHODS

Subjects

The study population consisted of a total of 349 Saudi subjects of either gender. The sample included 172 schizophrenia patients recruited from the outpatient psychiatric clinic of Riyadh Military Hospital (RMH), Riyadh, Saudi Arabia, and 177 age- and gender-matched healthy volunteers. All subjects were biologically unrelated Saudis. Among 172 confirmed cases of schizophrenia, 91 patients were with negative symptoms while 81 with positive symptoms. There were 49 females and 123 males with a mean age of 39 ± 12.5 years and mean disease duration of 9 ± 4.5 years, while age of onset of disease varied from 19 to 64 years. The female to male ratio of schizophrenia patients in our study was 1:2.5. The control group consisted of 50 females and 127 males with mean age of 35 ± 10.5 years.

The diagnosis of schizophrenia was based on the criteria mentioned in the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR Version. These criteria use the self-reported experience of the patient and reported abnormalities in behavior and a comprehensive clinical assessment by a neuropsychiatrist. If diagnosis of schizophrenia was confirmed by the above-mentioned criteria, patients were further assessed for positive and negative symptoms using Positive or Negative Syndrome Scale (PANSS) involving further clinical interview, cognitive testing, motor assessment, and careful review of medical and historical records as described by Kay et al. (1987). All subjects in the control group were screened using a questionnaire about the health status and excluded if they had any history of neurological, psychiatric or medical disorders or had a past or present involvement in substance abuse. None of the control subjects had a first- or second-degree relative with any mental illness. A number of baseline parameters to rule out any psychotic illness were adopted as described by Johnstone et al. (2005). Written informed consent was obtained from all subjects in accordance with ethical guidelines set by a local Ethics Committee.

Polymerase chain reaction (PCR) amplification

Genomic DNA was extracted from the blood of schizophrenia patients and controls using

the QIAamp^R DNA mini kit (Qiagen, USA). A genomic DNA fragment containing the Val¹⁵⁸Met polymorphism in the human COMT sequence (GenBank Accession No. AY 341246 with the SNP site being in the nucleotide 23,753 of this accession number) was amplified by PCR (Ruiz-Sanz et al., 2007). PCR amplification was carried out using Ready-to-Go PCR Beads (Amersham Biosciences, USA) in a Gradient Master Thermal Cycler (Eppendorf, Germany) with an initial denaturation at 94°C for 4 min followed by 30 cycles of 94°C for 30 s, 62°C for 30 s and 72°C for 20 s and a final extension at 72°C for 5 min. PCR products obtained were separated by electrophoresis on a 1.5% agarose gel in TAE buffer, visualized by ethidium bromide fluorescence. This procedure rendered 3 bands in heterozygotes (626, 451 and 222 bp) and 2 bands in homozygotes (Met¹⁵⁸Met resulting in 626 and 222 bp, and Val¹⁵⁸Val resulting in 626 and 451 bp).

Statistical analysis

The differences in genotype and allele frequencies between patients and controls were analyzed with the Fisher exact test using the CalcFisher software (<http://www.jstatsoft.org/v08/i21/paper>).

$P \leq 0.05$ was considered to be significant. The strength of the association of disease with respect to a particular genotype/allele are reported with the odds ratio interpreted as relative risk (RR) following the method of Woolf as described by Schallreuter et al. (1993). RR indicates how many times more frequent a disease is in the positive subjects compared with allele/genotype-negative subjects. It is calculated for a genotype/allele that is increased or decreased in schizophrenia patients compared to the frequency in normal Saudi subjects. RR was calculated for all the subjects using the following formula:

$$RR = (a \times d) / (b \times c)$$

(a) = number of patients expressing the allele or genotype

(b) = number of patients without allele or genotype expression

(c) = number of controls expressing the allele or genotype

(d) = number of controls without allele or genotype expression

The etiologic fraction (EF) indicates the hypothetical genetic component of the disease. EF values of >0.00-0.99 are significant. It is calculated for positive associations ($RR > 1$) using the following formula:

$$EF = (RR - 1)f / RR, \text{ where } f = a / a + c.$$

Preventive fraction (PF) indicates the hypothetical protective effect of one allele/genotype for a disease. It is calculated for negative associations ($RR < 1$) using the following formula. Values of <1.0 indicate the protective effect of an allele/genotype against the manifestation of disease.

$$PF = (1 - RR)f / RR (1 - f) + f, \text{ where } f = a / a + c.$$

RESULTS

The frequencies of genotypes and alleles of the Val¹⁵⁸Met polymorphism were obtained from schizophrenia patients and matched controls (Tables 1-5). In the patient group, there were 12 (6.98%) Val¹⁵⁸ homozygotes, 111 (64.53%) Val¹⁵⁸ Met heterozygotes, and 49

(28.49%) Met¹⁵⁸ homozygotes. The control group contained 54 (30.50%) Val¹⁵⁸ homozygotes, 71 (40.11%) Val¹⁵⁸Met heterozygotes, and 52 (29.38%) Met¹⁵⁸ homozygotes. The frequencies of genotype Val¹⁵⁸Val as well as Val¹⁵⁸Met differed significantly in patient and control groups ($P = 0.0001$). The genotype Val¹⁵⁸Val was predominant in controls, whereas the genotype Val¹⁵⁸Met was found to be increased in the patient group. Allele A (Met)-containing genotypes (GA+AA) were found in 93.02% of the patients and 69.49% of controls ($P = 0.0001$). The frequencies of both alleles also differed significantly in patients and the control group ($P = 0.0029$) and allele Met¹⁵⁸ was found to be associated with schizophrenia (RR = 1.583, EF = 0.200). The genotype Val/Met was significantly associated with schizophrenia ($P = 0.0001$, RR = 2.716, EF = 0.385). On stratification of the patients with negative or positive symptoms of schizophrenia and comparing with controls, a similar distribution pattern of alleles and genotypes was noticed in the two groups (Tables 2 and 3).

Table 1. Genotype and allele frequencies of the COMT (Val¹⁵⁸Met) polymorphism in schizophrenia patients and matched controls.

Genotype/ Allele	Schizophrenia (N = 172)		Control (N = 177)		P	RR	EF [†] /PF
	N	%	N	%			
GG (val/val)	12	6.976	54	30.508	0.0001*	0.170	0.469
GA (val/met)	111	64.534	71	40.112	0.0001*	2.716	0.385 [†]
AA (met/met)	49	28.488	52	29.378	0.9062	0.957	0.021
GA+AA	160	93.023	123	69.491	0.0001*	5.853	0.468 [†]
G-allele (val)	135	39.244	179	50.564	0.0029*	0.631	0.201
A-allele (met)	209	60.755	175	49.435	0.0029*	1.583	0.200 [†]

N = number of subjects; RR = relative risk; EF = etiological fraction; PF = preventive fraction. *Statistically significant.

Table 2. Genotype frequencies of the COMT (Val¹⁵⁸Met) polymorphism in schizophrenia patients with negative symptoms and controls.

Genotype	With negative symptoms (N = 91)		Control (N = 177)		P
	N	%	N	%	
GG (val/val)	7	7.692	54	30.508	0.0001*
GA (val/met)	57	62.637	71	40.112	0.0005*
AA (met/met)	27	29.670	52	29.378	0.999
G-allele (val)	71	39.01	179	50.564	0.013*
A-allele (met)	111	60.99	175	49.435	0.013*

N = number of subjects. *Statistically significant.

Table 3. Genotype and allele frequencies of the COMT (Val¹⁵⁸Met) polymorphism in schizophrenia patients with positive symptoms and controls.

Genotype	With positive symptoms (N = 81)		Control (N = 177)		P
	N	%	N	%	
GG (val/val)	5	6.173	54	30.508	0.0001*
GA (val/met)	53	65.432	71	40.112	0.0001*
AA (met/met)	23	28.395	52	29.378	0.9999
G-allele (val)	63	38.89	179	50.564	0.0173*
A-allele (met)	99	61.11	175	49.435	0.0173*

N = number of subjects. *Statistically significant.

Table 4. Genotype and allele frequencies of the COMT (Val¹⁵⁸Met) polymorphism in male schizophrenia patients and male controls.

Genotype/ allele	Patients (N = 123)		Controls (N = 127)		P	RR	EF [†] /PF
	N	%	N	%			
GG (val/val)	8	6.504	50	39.4	0.0001*	0.145	0.4486
GA (val/met)	85	69.105	47	37.0	0.0001*	3.807	0.4748 [†]
AA (met/met)	30	24.390	30	23.6	0.9999	1.043	0.0206 [†]
GA+AA	115	93.496	77	60.63	0.0001*	9.334	0.5339 [†]
G-allele (val)	101	41.057	147	57.87	0.0001*	0.507	0.2835
A-allele (met)	145	58.943	107	42.13	0.0001*	1.072	0.2834 [†]

N = number of subjects; RR = relative risk; EF = etiological fraction; PF = preventive fraction. *Statistically significant.

Table 5. Genotype and allele frequencies of the COMT (Val¹⁵⁸Met) polymorphism in female schizophrenia patients and female controls.

Genotype/ allele	Patients (N = 49)		Controls (N = 50)		P	RR	EF*/PF
	N	%	N	%			
GG (val/val)	4	8.163	4	8	0.999	1.0222	0.0108*
GA (val/met)	26	53.061	24	48	0.689	1.2246	0.0953*
AA (met/met)	19	38.775	22	44	0.684	0.806	0.1002
GA+AA	45	91.84	46	92	0.999	0.978	0.0109
G-allele (val)	34	34.69	32	32	0.763	1.1289	0.0588*
A-allele (met)	64	65.31	68	68	0.763	0.8858	0.0622

N = number of subjects; RR = relative risk; EF = etiological fraction; PF = preventive fraction.

The effect of gender on genotype and allele frequencies of the Val¹⁵⁸Met polymorphism in Saudi schizophrenia patients and control subjects is presented in Tables 4 and 5. We observed a significant difference in the frequencies of the Val/Met genotype between male (69.10%) and female (53.06%) patients. However, on comparison with controls of the same gender, female patients did not show a significant difference ($P = 0.689$) while male patients were found to have a very significant difference in the distribution of alleles as well as genotypes of the Val¹⁵⁸Met polymorphism ($P = 0.0001$). Gender difference was very significant and male patients had significant association with the Val¹⁵⁸Met polymorphism, while female patients did not (Tables 4 and 5). The association of the Val¹⁵⁸Met polymorphism with schizophrenia in different populations worldwide reported by various authors are compared in Table 6, which indicated quite conflicting results, and even the same populations such as Chinese, Caucasian and Japanese studied by different authors gave different results.

DISCUSSION

Our results of genotype and allele frequencies suggest that the COMT Val¹⁵⁸Met polymorphism has a significant association with schizophrenia in Saudis. Our findings are in agreement with several earlier studies on Chinese (Wang et al., 2010; Wan et al., 2011), Indian (Gupta et al., 2009), Malays (Wan et al., 2011), Japanese (Ohmori et al., 1998), and Israeli (Kotler et al., 1999) populations, which also observed a significant association between the Val¹⁵⁸Met genotype of the COMT polymorphism with schizophrenia.

Table 6. Association of the COMT (Val¹⁵⁸Met) polymorphism in etiopathogenesis of schizophrenia in various populations.

Population/group studied	Genotype/Allele	P values	References
Saudis	Val/Met	0.0001	Present study
Saudis	Met	0.0029	Present study
Caucasian	Val>Met	0.0015	Kunugi et al., 1997
Caucasian and African-American	Val	0.043	Wonodi et al., 2006
Caucasian	No association	0.37	Karayiogou et al., 1998
Caucasian	No association	0.20	Rosa et al., 2004
Chinese	Val/Met	-	Wang et al., 2010
Chinese	Val/Met	-	Wan et al., 2011
Chinese	No association	0.54	Fan et al., 2005
Chinese	No association	-	Kong et al., 2011
Han Chinese	No association	-	Kang et al., 2010a
Han Chinese	No association	-	Chen et al., 2011
Han Chinese	No association	0.11	Zhang et al., 2012
Malays	Val/Met	-	Wan et al., 2011
Indian	Val/Met	-	Wan et al., 2011
Indian	Val/Met	0.044	Gupta et al., 2009
Turks	Met/Met	0.001	Sazci et al., 2004
Israeli	Met	-	Kotler et al., 1999
Jewish (Israeli)	Val/Val	0.0074	Shifman et al., 2002
Syrian	No association	-	Lajin et al., 2011
Japanese	Met	0.028	Ohmori et al., 1998
Japanese	No association	-	Okochi et al., 2009
Spanish	Val/Met*	0.04	Lafuente et al., 2008
Spanish	Val/Met*	0.03	Hoенicka et al., 2010
Spanish	Val/Met*	0.023	Costas et al., 2011
Australian	Val/Val	-	Voisey et al., 2012
Polish	No association	-	Pawel et al., 2010
German	No association	-	Nieratschker et al., 2010
Korean	No association	-	Kang et al., 2010b

*Protective for schizophrenia.

On the other hand, a number of investigators have reported a lack of association between the Val¹⁵⁸Met genotype and schizophrenia in African-American (Wonodi et al., 2006), Chinese (Kang et al., 2010a; Chen et al., 2011; Kong et al., 2011), Caucasian (Rosa et al., 2004), Japanese (Okochi et al., 2009), Polish (Pawel et al., 2010), Korean (Kang et al., 2010b), and German (Nieratschker et al., 2010) populations.

In this study, we observed a highly significant association between the Met-COMT allele in Saudi patients with schizophrenia (Table 1). Our finding is in agreement with earlier reports by Ohmori et al. (1998), in Japanese, and Kotler et al. (1999), in Israeli population. The Met-COMT allele has also been reported to be associated with violent/aggressive behavior in schizophrenia (Tosato et al., 2011). Earlier, an association has been reported between the low-activity Met allele with fewer perseverative errors in the Wisconsin Card Sorting Test (WCST) and a more efficient task-related pattern of activation in the prefrontal cortex (PFC) in the control subjects as compared to schizophrenia patients. On the other hand, some other reports have suggested a significant association between the Val-COMT allele and susceptibility to schizophrenia (Shifman et al., 2002; Wonodi et al., 2006; Hoенicka et al., 2010; Voisey et al., 2010). Wonodi et al. (2006) estimated that the Val-COMT allele accounts for up to 23% of the burden of schizophrenia. It has been suggested that the Val-COMT allele is associated with poorer performances, compared to the Met-COMT allele, in cognitive tasks of prefrontal function. The underlying mechanism of such behavioral differences has been related to lower prefrontal dopamine levels arising from higher dopamine catabolism mediated by the Val-COMT allele (Chen et al., 2004).

Overall, the analysis of available data clearly shows inconsistent finding even in various inter- and intra-ethnic groups (Table 6) with no clear-cut evidence of positive or negative association between the COMT Val¹⁵⁸Met polymorphism and schizophrenia (Fan et al., 2005; Kang et al., 2010a,b). According to some investigators, this ambiguity in results may be attributed to functional state of disease such as violent/aggressive behavior (Kotler et al., 1999; Tosato et al., 2011), positive/negative symptoms (Wang et al., 2010; Li et al., 2012), age of onset, cognitive function, and severity of psychotic symptoms (Sagud et al., 2010).

In this study, we segregated schizophrenia patients according to their negative (91 patients) and positive symptoms (81 patients) based on criteria described by Kay et al. (1987). Although both groups of patients with negative and positive symptoms had similar significant association with the Val¹⁵⁸Met COMT polymorphism, there was no significant difference between the genotype frequencies between these two groups. Our finding is in agreement with Strous et al. (2006) who suggested that COMT genotypes are not related to the clinical symptomatology of schizophrenia. A potential explanation for this lack of association between Val¹⁵⁸Met COMT polymorphism with either negative or positive symptoms has been attributed to the fact that some other modifying genes may be involved, which may be responsible for the manifestation of positive and negative symptoms in the clinical expression of schizophrenia. Thus, the effect of COMT on various symptom expressions may not necessarily be generalized. Further studies are certainly mandated to investigate the relationship in a large patient cohort to investigate various unproven hypotheses.

The effect of gender on genotype and allele frequencies of the Val¹⁵⁸Met polymorphism in Saudi schizophrenia patients and control subjects was very clear. We observed a significant difference in the frequencies of the Val/Met genotype between male and female patients. However, on comparison with controls of the same gender, female patients had no association while male patients were found to have a very significant association with the Val¹⁵⁸Met polymorphism ($P = 0.0001$). Our findings are in agreement with earlier studies that observed an effect of gender on the COMT Val¹⁵⁸Met polymorphism (Kempton et al., 2009). Gender-specific genetic component in schizophrenia has been suggested by Shifman et al. (2002). Contrary to these findings, a twin study failed to find evidence of specific gender effects for schizophrenia, perhaps reflecting the low statistical power of that approach (Shifman et al., 2002). The gender-specific phenotypic differences observed in patients with schizophrenia may reflect the distinction between males and females in the etiology of schizophrenia due to difference in COMT activity. It has been observed that females have 20-30% lower COMT activity as compared to males perhaps due to down regulation of COMT by estrogen in females (Coman et al., 2010). Hence, the Val¹⁵⁸Met polymorphism may be mediated by gender. At present, there is very limited data to elucidate the multifaceted interplay between the COMT polymorphism and gender. Further studies are warranted to determine the role of gender in the COMT polymorphism in schizophrenia and other dopamine-regulated disorders.

In summary, this study provides evidence for an association between the COMT Val¹⁵⁸Met polymorphism and schizophrenia in the Saudi population. Our data further suggest that gender exerts a significant effect on the frequency distribution of genotypes and alleles of the COMT Val¹⁵⁸Met polymorphism while disease manifestation such as positive or negative symptoms has no significant impact on it.

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