Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.16.006

Catechol-O-methyltransferase (COMT) Val158Met polymorphism in schizophrenia patients: response to antipsychotic treatment and cognitive function

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Submitted: 21 April 2023; Accepted: 17 May 2023; Published: 06 June 2023

ABSTRACT

Schizophrenia is a complex and severe mental disorder, suggesting genetic factors involvement. The role of Catechol-O-methyltransferase (COMT) gene in the degradation of dopamine could be related to treatment response to antipsychotics and cognitive functions in schizophrenia. This study investigated the association between genotypic polymorphisms of COMT Val158Met and treatment response to risperidone and cognitive function in schizophrenia patients. By using cross-sectional study, this study recruited 200 subjects and later divided them into 2 groups. The first group consisted of 100 subjects with schizophrenia and the second group consisted of 100 healthy volunteers. Clinical improvement of schizophrenia group assessed thrice in 4 weeks (on admission, on the 2nd, and 4th week) using the PANSS Score. The cognitive test in the schizophrenia group was assessed in the 4th week using TMT. The results found that individuals with the Met allele have a 3.353 times risk for schizophrenia. PANSS positive score tends to higher in schizophrenia with Met allele whereas PANSS negative score tends to higher in Val/Val genotype on admission. Schizophrenia with Met allele tends to finish the test faster TMT A and TMT B than to Val / Val genotype. Even though no significant association, schizophrenia with Met allele tends to have a better treatment response and cognitive function compared to Val/Val genotype. This study concluded that COMT Val158Met polymorphism has an influence on treatment response to risperidone and cognitive function in schizophrenia.

Keywords: *COMT Val158Met polymorphism, risperidone, schizophrenia, treatment response, cognitive function*

INTRODUCTION

Schizophrenia along with other psychotic disorders are characterized by several psychopathological domains include positive symptoms, negative symptoms, disorganization, cognitive impairment, motor symptoms, and mood symptoms, patterns of treatment-response, and prognostic implications [1]. Schizophrenia is a complex and severe disorder affecting 1% of the population, with high heritability, estimated around 80%, suggesting a strong involvement of genetic factors.

Moreover, schizophrenia is associated with considerable disability and may affect educational and occupational performance which involved their treatment response to antipsychotic and impaired cognitive function [2].

Although antipsychotics play a critical role in the treatment of schizophrenia, there are considerable differences in the treatment response to antipsychotics. Several candidate genes have been explored in pharmacogenomics studies of treatment response in schizophrenia [3]. Previous studies showed significant association between the treatment response to antipsychotics and *DRD1 rs265976* polymorphisms [4], DRD2 141-C Ins/Del Receptor polymorphisms [5], 5-HT(2A) HTR2C polymorphisms, particularly Cys23Ser [6].

Impaired cognitive function has a high consequence in schizophrenia [7]. Learning/memory deficits were observed even in schizophrenia with less severe generalized deficit. The executive and attentional deficits evident in the more severely disabled in schizophrenia [8].

The Catechol-O-methyltransferase (COMT) gene is one of the investigated candidate genes for schizophrenia because of its role in the degradation of dopamine. The COMT gene located in chromosome 22q11 codes for an enzyme that degrades catecholamines, including dopamine, which account for a three-to-four-fold variation in enzyme activity [9].

In recent studies showed that the COMT Val158Met polymorphism could be related to treatment response to typical and atypical antipsychotics [10-12], and influences cognitive functions in schizophrenia [13-16]. To the best of our knowledge, there is a lack of data in Indonesia regarding the role of genes in the incidence, treatment response, and cognitive function of schizophrenia, we investigated the association between genotypic polymorphisms of COMT Val158Met and treatment response to risperidone and cognitive function in schizophrenia patients.

SUBJECTS AND METHODS

This cross-sectional involved two hundred subject's alternative: in this cross-sectional study, we recruited 200 subjects and later divided them into 2 groups. The sample size is calculated based on the following formula:

$$n = \frac{2\partial^2 (Z1-\alpha/2 + Z1-\beta)^2}{(X1-X2)^2}$$

$$= \frac{2x20^2 (1-5/2 + 90)^2}{(50-40)^2}$$

$$= 85$$

Note: α = Level of significance (%); 1-β= Power of test (%); ∂ = Population standard deviation; X1= Test value of the population mean; X2= Anticipated of the population mean; n= Sample size

Thus, the sample size for each sample group is 85 people which is rounded up to 100 for each group [17]. The first group consisted of 100 subjects with schizophrenia in the "Dadi" Mental Hospital of South Sulawesi (Makassar, Indonesia). Inclusion for the first group required a combination of criteria including diagnosis of schizophrenia according to DSM-V by the attending psychiatrist, being treated with risperidone within therapeutic dose range (2 to 4 mg); and ranging from 18 to 40 years of age. The second group consisted of 100 healthy volunteers ranging from 18 – 40 years of age with neither history of psychiatric disorders nor family history of psychiatric disorders. The inclusion criteria for healthy people were aged 20-50 years, did not experience severe mental disorders, and did not have a family history of severe mental disorders. As exclusion criteria, all subjects in both groups were without any known history of substance abuse, brain diseases, medical condition, or medication that was known to have neuropsychological consequences. Both groups gave their written informed consent and were studied under a protocol approved by the Hasanuddin University Medical Ethic Committee (No. 623/UN4.6.4.5.31/ PP36/ 2020).

Clinical improvement of schizophrenia group assessed thrice in 4 weeks (on admission, on the 2nd, and 4th week) using the Positive and Negative Symptom Scale (PANSS) Score. Treatment response divided into two categories, poor and good response. Poor response identified as $\leq$ 40% PANSS score reduction from baseline to the 4th week. Good response identified as > 40% PANSS score reduction from baseline to the 4th week. Cognitive test in the schizophrenia group was assessed in the 4th week using The Trail

Making Test (TMT). An average score for TMT-A is 29 seconds and a deficient score is greater than 78 seconds. For TMT-B, an average score is 75 seconds and a deficient score is greater than 273 seconds [18].

Venous blood samples (3 ml) were collected in ethylenediaminetetraacetic acid (EDTA) containing tubes. We conducted an allele-specific polymerase chain reaction (PCR) based restriction fragment length polymorphism (PCR-RFLP) to genotype for COMT Val158Met. The primers forward 5'-CGAGGCTCATCACCATCGAGATC -3' and reverse 5'-CTGACAACGGGTCAGGAATGCA -3' were used in this study. PCR tubes were inserted into the PCR machine and set up the machine. Pre denaturation at 94°C for 5 minutes followed by 32 cycles of 94°C for 30 seconds (Desaturase), 62°C for 30 seconds (Annealing), 72°C for 10 seconds (Extension), and final extension 72°C for 5 minutes. The RFLP with NIaIII enzyme. Then electrophoresis of 2% agarose was performed with ethidium bromide. Met/Met was represented by the uncut 72 and 36 bp, Val/Val was represented by the uncut 108 bp, Val/Met was represented by the uncut 108, 72, and 36 bp. Statistical analysis was performed using the SPSS ver. 22.0 for Windows. Chi-squared and Mann-Whitney tests were used for the statistical analyses of the data.

RESULTS

We divided our subjects into two groups: the schizophrenia group and the healthy volunteer's group, with characteristics described and compared in Table 1. The schizophrenia group included 100 subjects (84 males and 16 females), with a mean age of 35.19 ± 7.72 years and the healthy volunteers group included 100 subjects (70 males and 30 females), with a mean age of 31.15 ± 8.05 years. We found three types of genotype in both group: in the schizophrenia group was 7% for Met/Met, 16% for Val/Met, and 77% for Val/Val, and those in the healthy volunteer group were 2% for Met/Met, 6% for Val/Met, and 92% for Val/Val. The distribution of allele frequencies of the COMT Val158Met polymorphism in the schizophrenia group was 15% for Met and 85% for Val, and those in the healthy volunteer group were 5% for Met and 95% for Val (Table 1).

TABLE 1: Demographic characteristics of the schizophrenia and the healthy volunteer's group

	Schizophrenia n = 100	**Healthy volunteers n = 100**
Age (years) mean ± SD	32.19 ± 7.72	31.15 ± 8.05
Sex		
Male	84 (84 %)	70 (70%)
Female	16 (16%)	30 (30%)
Genotype		
AA (Met/Met)	7 (7%)	2 (2%)
GA (Val/Met)	16 (16%)	6 (6%)
GG (Val/Val)	77 (77%)	92 (92%)
Allele		
A (Met)	30 (15%)	10 (5%)
G (Val)	170 (85%)	190 (95%)

*primary data 2020

The COMT allele frequency was significantly distributed between schizophrenia and healthy volunteers. The Met allele was 15% in schizophrenia and 5% in healthy volunteers. Individuals with the Met allele had an even more increased risk for schizophrenia (OR = 3.353; 95% CI 1.592-7.063; p <0.001) (Table 2).

TABLE 2: Association between allele in schizophrenia and healthy volunteer's group

	Schizophrenia n = 100	**Healthy volunteers n = 100**	**OR**	**95% CI**		**p value**
				Lower	**Upper**	
Allele						
Met	30 (15%)	10 (5%)	3.353	1.592	7.063	<0.001*
Val	170 (85%)	190 (95%)				

*Chi Square OR = Odds Ratio CI Confidence Interval

Although our results shown no significant difference between schizophrenia patients with Met allele (Met/Met genotype + Val/Met genotype) and Val/Val genotype with p>0.05, but we found that on admission, PANSS positive score tend to higher in schizophrenia with Met allele (Met/Met genotype + Val/Met genotype) (31.56 ± 2.55) compare to Val/Val genotype (31.19 ± 2.29), whereas PANSS negative score tend to higher in Val / Val genotype (22.45 ± 3.79) compare to schizophrenia with Met allele (Met/Met genotype + Val/Met genotype) (20.87 ± 3.10) (Table 3).

TABLE 3: Association between PANSS score and COMT Val158Met polymorphism

PANSS	**Met/Met + Val/Met Mean ± SD**	**Val/Val Mean ± SD**	**p value**
on admission			
PANSS Positive	31.56 ± 2.55	31.19 ± 2.29	0.746
PANSS Negative	20.87 ± 3.10	22.45 ± 3.79	0.068
PANSS General	49.39 ± 4.12	51.00 ± 5.99	0.327
PANSS Total	101.826 ± 8.18	104.64 ± 9.51	0.210
on the 2nd week			
PANSS Positive	21.43 ± 2.55	21.41 ± 2.72	0.833
PANSS Negative	17.26 ± 3.82	19.10 ± 4.24	0.032*
PANSS General	38.61 ± 5.46	40.63 ± 5.69	0.70
PANSS Total	77.30 ± 11.21	81.15 ± 11.55	0.077
on 4th week			
PANSS Positive	17.65 ± 3.31	17.74 ± 3.89	0.911
PANSS Negative	16.22 ± 2.87	17.89 ± 4.38	0.097
PANSS General	31.18 ± 7.29	34.23 ± 9.06	0.140
PANSS Total	65.04 ± 12.23	70.02 ± 16.36	0.197

PANSS = Positive and Negative Symptom Scale *p<0,05 (Uji Mann Whitney test), primary data 2020

Our results shown that schizophrenia with Met allele (Met/Met genotype + Val/Met genotype) tend to have a better treatment response in PANSS positive (73.9%), PANSS general (60.9%) and PANSS total (43.5%) compare to Val/Val genotype, even though no significant association between the treatment response and the COMT Val158Met polymorphism with p >0.05 (Table 4).

TABLE 4: Association between treatment response and COMT Val158Met polymorphism

Genotype	**Treatment Response**		**p value**
	Poor response	Good response	
PANSS Positive			
Met/Met + Val/Met	6 (26.1%)	17 (73.9%)	0.618
Val/Val	25 (32.5%)	52 (67.5 %)	
PANSS Negative			
Met/Met + Val/Met	22 (95.7%)	1 (4.3%)	0.705

Val/Val	72 (93.5%)	5 (6.5%)	
PANSS General			
Met/Met + Val/Met	9 (39.1%)	14 (60.9%)	0.234
Val/Val	43 (55.8%)	34 (44.2%)	
PANSS Total			
Met/Met + Val/Met	13 (56.5%)	10 (43.5%)	0.813
Val/Val	46 (59.7%)	31 (40.3%)	

PANSS = Positive and Negative Symptom Scale * p<0,05 (*Chi-Square*), primary data 2020

Out of 100 subjects in schizophrenia group, only 69 subjects could complete the TMT-A and TMT-B tests and there was no significant difference between the COMT Val158Met gene polymorphisms and time to complete the test (p> 0.05). However, schizophrenia with Met allele (Met/Met + Val/Met) (TMT A 99.17 ± 43.39; TMT B 190.65 ± 69.48) tend to finish the test faster than to Val / Val genotype (TMT A 116.33 ± 74.45; TMT B 224.06 ± 112.27). Our finding shown that there was no significant association between cognitive function and COMT Val158Met polymorphism (p> 0.05), but schizophrenia with Met allele (Met/Met + Val/Met) (no deficient : 52.9% in TMT A and 64.7% in TMT B) tend to have a better cognitive function in both compare to Val/Val genotype (no deficient : 42.3% in TMT A and 55.8% in TMT B) (Table 5).

TABLE 5: Association between cognitive function and COMT Val158Met polymorphism

Variable	**Genotype**	**Time (second) Mean ± SD**	**p values***	**Cognitive Function**		**p values****
				No deficient	deficient	
TMT A	Met/Met + Val/Met	99.17 ± 43.39	0.448	9 (52.9%)	8 (47.1%)	0.576
	Val/Val	116.33 ± 74.45		22 (42.3%)	30 (57.7%)	
TMT B	Met/Met + Val/Met	190.65 ± 69.48	0.611	11 (64.7%)	6 (35,3%)	0.581
	Val/Val	224.06 ± 112.27		29 (55.8%)	23 (44.2%)	

TMT = The Trail Making Test *signifikan p<0,05 (Mann Whitney study) and **signifikan p<0,05 (Chi-Square study)

As comparison, the study performed the relationship between TMT-A and TMT-B with the COMT Val158Met Gene Polymorphism in the healthy group.

TABLE 6: Comparison of the timing of TMT A and TMT B polymorphisms of the COMT Val158Met gene in a group of healthy people

Variable	**Genotype**	**Time (seconds) Median (min-max)**	**p-value**
TMT A	Met/Met	35 (26-44)	0.168
	Val/Met	32 (26-64)	
	Val/Val	28 (13-82)	
TMT B	Met/Met	50.5 (50-51)	0.108
	Val/Met	72 (44-93)	
	Val/Val	54 (13-159)	

*significant at p<0,05 (Mann Whitney test)

Table 6 on the results of TMT-A and TMT-B there was no significant difference between the Met/Met, Val/Met, Val/Val genotypes and the time to complete the test (p > 0.05). However, in TMT-A Val/Val genotypes tend to finish the test better than other genotypes, while in TMT-B Met/Met genotypes tend to finish the test longer than other genotypes.

TABLE 7: Relationship of the COMT Val158Met gene polymorphism with cognitive function in a group of healthy people

Genotype	Cognitive Function		p-value
	Mean (< 78 second)	Decline (> 78 second)	
TMT A			
Met/Met + Val/Met	2 (25%)	6 (75%)	0.50
Val/Val	56 (60.9%)	36 (39.1%)	
TMT B			
Met/Met + Val/Met	7 (87.5%)	1 (12.5%)	0.582
Val/Val	73 (79.3%)	19 (20.7.1%)	

**significant at p<0,05 (Chi-Square test)

The results as presented in Table 7 showed that there was no significant relationship between cognitive function and genotype (p > 0.05). In TMT-A, the Met allele has cognitive function that tends to be worse, while in TMT-B the non-Met allele has cognitive function that tends to be worse.

DISCUSSION

Our finding showed there was a significant difference between allele and genotype COMT Val158Met polymorphism in schizophrenia in comparison to healthy volunteers which in line with several earlier studies on Malays and Saudis [19, 20]. We detected Val allele more frequent in both schizophrenia and healthy volunteers. However, Met allele is significantly more common in schizophrenia than in healthy volunteers. According to this finding, we suggested that Met allele has a 3.353-fold increased risk for schizophrenia. Study by Sazci A et al, also found that Met genotype had a 1.818-fold increased risk for schizophrenia OR=1.818 in men and a 2.456-fold increased risk for schizophrenia OR=2.456 in women [21]. Dysregulation in the dopamine signalling may be a risk factor in the development of schizophrenia due to COMT polymorphism produces too high and too low levels of dopamine [22]. The Met allele is associated with low enzymatic activity and the Val allele is associated with high enzymatic activity. Met homozygotes yield a three to four-fold reduction in COMT activity relative to Val homozygotes, with heterozygotes demonstrating intermediate activity [8, 9].

Although our results showed no significant association between schizophrenia with COMT Val158Met polymorphism and PANSS score, PANSS positive score tend to be higher in schizophrenia with Met allele and PANSS negative score tend to be higher in Val / Val genotype before treatment. In the prefrontal cortex, the activity of Met homozygotes results in a fourfold reduction in COMT enzyme activity and caused a hyperdopaminergic state in the mesolimbic dopamine pathway influences the regulation of emotional behaviors and positive symptoms like delusions and hallucinations. Whereas, activity Val homozygotes results in three times higher COMT enzyme activity caused hypodopaminergic state in the mesocortical dopamine pathway and influences the cognitive, negative, and affective symptoms of schizophrenia [9, 23]. Several studies have suggested a relationship between the COMT Val158Met polymorphism and both positive and negative symptoms in schizophrenia. COMT lower carrier (Met allele) had higher attention, delusion scores, verbal aggression, and lower inappropriate affect scores than COMT high homozygote (Val/Val) [24, 25, 26]. While COMT high homozygote (Val/Val) higher negative symptoms of PANSS than COMT lower carrier (Met allele) [27, 28].

In the former studies there are contradictory results that the COMT Val158Met polymorphism could be related to treatment response to antipsychotics. COMT genotype does not significantly influence the efficacy of risperidone [12]. On the contrary, Met allele may be associated with unsatisfactory drug response to typical antipsychotic [10]. Moreover, Val/Val patients with schizophrenia showed a worse response to the neuroleptic treatment [11, 29]. According to the tonic-phasic dopamine hypothesis, the Met allele caused decreased phasic and increased tonic dopamine transmission subcortically, surges dopamine concentrations cortically, boosted D1 and

reduced D2 transmission, and the Val allele does the other way around [8, 30]. The results of this study suggested that Met allele tends to give a better treatment response to risperidone than the Val / Val genotype. Activity Met allele due to lower phasic dopamine transmission subcortically associated with greater dopamine synthesis in the midbrain, lower striatal dopaminergic stimulation, increased D1 receptor activation, increased glutamate release from pyramidal neurons onto the nucleus accumbens. This matter potentiates the effects of antipsychotic-induced D2 receptor blockade and thus reducing positive symptom severity [8, 30, 31]. Several studies with atypical antipsychotics showed analogous results to our findings. The COMT Met allele had a better response after treatment with olanzapine, clozapine and, aripiprazole [32, 33, 34].

Cognitive impairment considered to be a central feature of schizophrenia. One of the cognitive deficits in schizophrenia is in the executive function and for this purpose we used TMT A and B. TMT A measures primarily visuoperceptual capabilities, while TMT B shows primarily working memory and secondarily task-switching capability, while B-A diminishes visuoperceptual and working memory burdens, delivering a relatively pure display of executive function [35]. We found no significant differences between the COMT Val158Met polymorphism with TMT A and TMT B performance, however Met allele tends to have better performance compare to Val allele. Several studies showed that performance on the TMT A and TMT B has no significant association with the COMT Val158Met polymorphism in patients with schizophrenia but Val/Val and Val/Met have worse performance [14,15,16]. Moreover, Met allele was associated with better performance in neurocognitive tests [8, 36, 37, 38]. In the prefrontal cortex, greater inactivation of enzymatic degradation by COMT caused lower dopamine transporter (DAT) activity. The "dual state" theory indicates that D1 and D2 receptors oppose each other, D1 expression predominates in the prefrontal cortex and generates their effects in cognitive function. Met allele is associated with higher dopamine level, predicting a more optimal D1/D2 balance, and Val allele associated with lower dopamine level and predicting a low D1/high D2 state [39, 40]. Several studies of antipsychotics showed improved cognition (or prevented its deterioration) among psychiatric populations mostly associated with Met allele homozygotes due to better-optimized D1/D2 balance and increase cortical D1 binding, although this pattern of results might seem counterintuitive. Reduced cortical D1 function is one possibility of results may differentially impact D1/D2 balance among individuals with schizophrenia spectrum disorders [40, 41]. In schizophrenia spectrum disorders patients may be shifted leftward on the inverted-U-shaped function, leaving Met allele homozygotes D1/D2 balance on the near left edge of the function and amenable to antipsychotic effects, but val-allele homozygotes balance so dysregulated that antipsychotics cannot remediate it [40]. Several studies found a significant association between COMT Val158Met polymorphism with antipsychotic treatment response which have been observed in 6 weeks, 8 weeks and, 12 weeks [32, 33, 34]. Other studies found a significant association between cognitive tests after 4 and 8 weeks after antipsychotic treatment [36, 37]. In our study, we observed an association between treatment response and cognitive function with COMT Val158Met polymorphism in 4 weeks.

CONCLUSION

This study concluded that COMT Val158Met polymorphism has an influence on treatment response to risperidone and cognitive function in schizophrenia. More specifically, the results statistically showed no significant association however we found a tendency to a risk factor for schizophrenia in Met allele, but with better treatment response and cognitive function. This study presumed that one of the constraints of this study is the short observational time, which may cause statistically insignificant result.

ACKNOWLEDGEMENT

The authors would like to thank Prof. Andi Jayalangkara Tanra, MD, PhD, Burhanuddin Bahar, MD, Ph.D, Kristian Liaury, MD, Ph.D, Firdaus Hamid, MD, Ph.D, Irfan Idris, MD, Ph.D, Musfiqoh Tusholehah, MD, Dewi Nofianti, MD, Ottorian Palinggi, MD, Syafri, and Research Laboratory of Hasanuddin University Hospital, as well as all the participating medical residents of Universitas Hasanuddin. The authors

are also grateful to all participating patients and their families.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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