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No association of Catechol-O-Methyltransferase (COMT) Gene Haplotypes in Patients with Schizophrenia in a Turkish Sample

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ABSTRACT:

No association of catechol-O-methyltransferase (COMT) gene haplotypes in patients with schizophrenia in a Turkish sample

Objective: The dopaminergic system, especially variations in the catechol-O-methyltransferase (COMT) gene, is of major interest in the etiology of schizophrenia. The rs4680 (Val108/158Met), rs165599, and P2 promoter rs2075507 single nucleotide polymorphisms (SNPs) in the COMT gene have been shown to be associated with alteration of COMT gene expression and COMT enzyme activity. The aim of this study was to investigate a possible association between schizophrenia and the haplotypes of these polymorphisms.

Methods: The sample was comprised of 181 patients with schizophrenia and 368 healthy controls. The patients' psychotic symptoms were rated using the Positive and Negative Symptom Scale (PANSS). COMT rs2075507, rs4680, and rs165599 SNPs were evaluated by a polymerase chain reaction, followed by restriction fragment length polymorphism analysis. These SNPs in the COMT gene were subjected to haplotype analyses using Haploview ver. 4.2.

Results: No significant differences were found between COMT rs2075507, rs4680, and rs165599 SNPs in schizophrenic patients and controls. The patients' PANSS results were not associated with these SNPs. No associations were obtained between 2 and 3-haplotypes of rs2075507, rs4680, rs165599 SNPs and schizophrenia.

Conclusion: COMT rs2075507, rs4680, rs165599 SNPs and haplotypes do not appear to be risk factors for schizophrenia in this population.

Keywords: COMT, gene, polymorphism, haplotypes, schizophrenia

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INTRODUCTION

Schizophrenia occurs in about 1% of the population worldwide and causes severe disability, but a comprehensive explanation of the etiology of schizophrenia has not yet emerged[1,2]. Chromosomal linkage studies have determined a risk for schizophrenia on chromosome 22q11.2[3], and this chromosomal location has the microdeletion found in velo-cardio-facial syndrome, which is associated with a high incidence of schizophrenia[4,5]. The catechol-O-methyl-transferase (COMT) gene is also located in chromosomal region 22q11.2. This COMT enzyme has a central role in the metabolism of dopamine and noradrenaline[6]. The most widely investigated functional polymorphism in the COMT gene is rs4680[7-10]. The Val(108/158)Met amino acid exchanges and induces enzyme activity change (approximately 40%) in the brain and lymphocytes[7]. Other functional variants independently affecting gene activity in the COMT gene are rs2075507 (previously rs2097603), linked upstream in the P2 promoter, and rs165599 in the 3' untranslated region[11,12]. The functional variant rs2075507 drives transcription of the predominant form of COMT in the brain, affects COMT activity in

lymphocytes and post-mortem brain tissue[11] and predicts changes in hippocampal gray matter volume in healthy volunteers[13]. The rs165599 is another variant in the 3' untranslated region, which is found to differentially affect the expression of rs4680 (Val(108/158)Met) alleles in human brain tissue[12] and is highly associated with schizophrenia in a large sample of Ashkenazi Jews[14]. Meyer-Lindenberg et al.[15] demonstrated a single nucleotide polymorphism (SNP) haplotype of rs2075507, Val(108/158)Met and rs165599 that was highly significantly associated with prefrontal cortex efficiency, which is consistent with Egan et al.'s[16] hypothesis of hypofrontality in schizophrenia. However, the association of these functional SNPs (rs2097603, rs4680, rs165599) and their haplotypes with schizophrenia remains unclear because some studies have reported a high association[14,17-20], but others have not[21-23].

In the present study, we investigated the association between schizophrenia and rs2075507, rs4680, and rs165599 functional polymorphisms in the COMT gene and 2-SNP and 3-SNP haplotypes of these polymorphisms in schizophrenia patients and a sample of healthy participants from the general population of Turkey. To our knowledge, this is the first study to investigate rs2075507 and 165599 polymorphisms and 2-SNP and 3-SNP haplotypes of rs2075507, rs4680, and rs165599 polymorphisms in the COMT gene in Turkish patients with schziophrenia.

MATERIALS AND METHODS

Sample of Study

One hundred and eighty one patients with schizophrenia were recruited from inpatient and outpatient units of the Psychiatry Department of Adnan Menderes University Medical Faculty Research Hospital in Aydin, Turkey. The diagnosis of patients was made using the Structured Clinical Interview according to DSM-IV criteria (American Psychiatric Association, 1994). Exclusion criteria were neurological or medical disease, mental retardation, substance abuse, toxic psychosis, or cognitive damage. The Positive and Negative Symptom Scale (PANSS) was also administered to the patients to assess their current symptoms. A mean PANSS positive subscale of 9.80±5.27 (7-31), a mean PANSS negative subscale of 12.41±5.93 (7-40), a mean PANSS general psychopathology score of 22.55±6.67 (13-58), and a mean PANSS total of 43.68±14.64 (30-124) were obtained from patients. Mean duration of illness of patients was 12.35 ± 9.33 years (0.5-48), mean age at onset of illness was 24.18±8.95 years (7-50), and there was no statistical differences in mean age at onset of schizophrenia between men and women (p>0.05). In our study, 50.8% (n=91) of patients reported a positive family history of schizophrenia.

Healthy controls (n=368) were recruited from individuals in the general population, who had no personal or familial history of psychotic disorder. They were also assessed using the Structured Clinical Interview for the DSM-IV to rule out any psychiatric disorder past or present. The Ethics Committee of the Faculty of Medicine of Adnan Menderes University approved the study protocol. All patients and control subjects gave their informed consent.

DNA Isolation and Genotyping

10 ml of venous blood was obtained from every subject by peripheral venous aspiration. DNA was isolated with a commercially available DNA-isolation kit (Quiagen Corp., Germany). Polymerase chain reactions (PCR) for rs2075507, Val(108/158) Met and rs165599 polymorphisms were performed as described elsewhere with slight modifications[24-28]. Localization of the selected SNPs in the COMT gene (rs2075507, Val(108/158)Met, and rs165599) is illustrated in Figure 1. The PCR reaction was carried out in a 25 µl volume containing 150 ng genomic DNA, 10 pM of each primer (Fermantes, Italy), 200 µM of each dNTP (Promega, USA), and 1×PCR reaction buffer that contained 40 mM KCl, 10 mM Tris-HCl (pH 8.3), 1.5 mM MgCl2, and 1 U of Taq Hot-start Polymerase (DNA Helix, South Korea). Primers (Fermantes, Italy) used in the PCRs were 5'-CTC TGG CGG AAA GGA AT-3' and 5'-TCG GCA

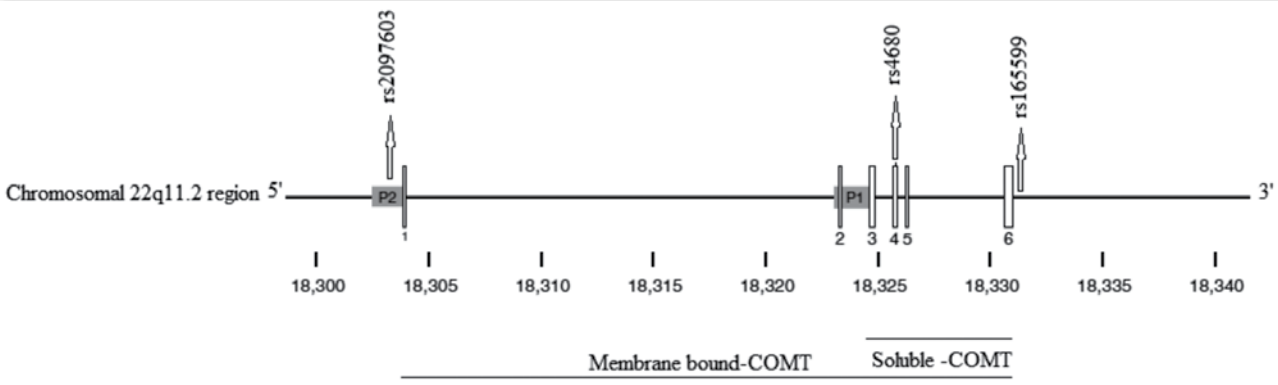

Figure 1: Location of the rs2097603, rs4680 and rs165599 SNPs in COMT gene on 22q11.2 region.

TCA AAA GGA GGA AAA AG-3 for rs2075507; F:5-TCG TGG ACG CCG TGA TTC AGG-3 R:5-AGG TCT GAC AAC GGG TCA GGC-3 for Val(108/158)Met; and F:5-GAA GGA GAT GCT TCC ACT CTG T-3 R:5-ACA TTC AAA GCT CCC CTT GAC-3 for rs165599. The PCRs were conducted after an initial step of 5 min at 95°C, 35 cycles of amplification (30 s at 95°C, 30 s at 54-65°C depending on primers Tm, 30 s at 72°C) and a final extension step of 10 min at 72°C. The PCR products were digested using restriction enzymes (Fermantes, Italy): Hind3 for COMT rs2075507, Nla III for Val(108/158)Met, and MspI for rs165599. Fragments were then separated in 2-3.5% agarose gels and subsequently stained with ethidium bromide and visualized under ultraviolet illumination.

Statistical Analysis

Categorical variables and differences in genotype and allele frequencies between groups were tested using the chi square test. Student t analysis was used for continuous variables. The Hardy–Weinberg equilibrium was tested by the chi-square test for goodness of fit. Single nucleotide polymorphisms in the COMT gene were subjected to haplotype analyses using Haploview ver. 4.2 (http:// www.broad.mit.edu/mpg/haploview/). The significance used in the analyses was defined as $p<0.05$. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS for Windows, Release 16, Chicago, IL).

RESULTS

Genotype frequencies were in Hardy-Weinberg equilibrium in the controls (χ^2=0.266, p=0.605 for rs4680; χ^2=0.191, p=0.661 for rs2075507; and χ^2=1.173, p=0.278 for rs165599), and in the patients (χ^2=0.549, p=0.458 for rs4680; χ^2=2.760, p=0.096 for rs2075507; and χ^2=0.329, p=0.565 for rs165599). Sociodemographic characteristics and the frequencies of the COMT P2 promoter rs2075507, rs4680, and rs165599 SNPs in the patients and control groups are presented in Table 1. No significant differences, either in genotypes or in allele frequencies of rs2075507, rs4680, and rs165599 SNPs, were observed between groups. There were no significant associations between these SNPs and the PANSS scale (p=0.964 for 2075507; p=0.314 for rs4680; p=0.424 for165599), age of onset of disease (p=0.764 for 2075507; p=0.692 for rs4680; p=0.985 for 165599) or the familial schizophrenia sub-group of patients (p=0.089 for 2075507; p=0.312 for rs4680; p=0.309 for 165599).

Analysis of pair-wise linkage disequilibrium (LD) of all SNPs was calculated using the Haploview and 4.2 application (Table 2 and Figure 2). The two and three-SNP haplotypes consisting of rs2075507, rs4680and rs165599 showed no difference between schizophrenia patients and controls (all data not shown), but the haplotype consisting of the G-G-A allele had a non-significantly higher frequency in control subjects than in schizophrenic patients (p=0.063).

Table 1: Sociodemographic characteristics and the frequencies of the COMT P2 promoter rs2075507, Val(108/158) Met and rs165599 polymorphisms in the patients and control groups

	Controls (n=368)	Patients (n=181)	P
Gender(Female/Male) N(%)	164(44.6)/204(55.4)	74(40.6)/107(59.4)	χ^2=0.792,df=1, p=0.374
Age (Mean±SD)	35.7±11.4	36.3±10.6	t=-0.850,df=541, p=0.396
Education (year) (Mean±SD)	10.7±4.4	7±4.5	t=8.914,df=524, p<0.001
COMT rs4680 (n,%)			
Val/Val	119 (32.7)	55 (30.4)	χ^2=0.802,df=2, p=0.670
Val/Met	174 (47.8)	85 (47)	
Met/Met	71 (19.5)	41 (22.7)	
Val	412 (56.8)	195 (53.9)	χ^2=0.833,df=1, p=0.362
Met	316 (43.2)	167 (46.1)	
COMT P2 promoter rs2075507 (n,%)			
AA	140 (38.6)	82 (45.3)	χ^2=3.293,df=2, p=0.193
AG	174 (47.9)	72 (39.8)	
GG	49 (13.5)	27 (14.9)	
A	459 (62.7)	236 (65.2)	χ^2 =0.647,df=1, p=0.421
G	273 (37.3)	126 (34.8)	
COMT rs165599 (n,%)			
AA	134 (36.7)	56 (32.6)	χ^2=1.203,df=2, p=0.548
AG	166 (45.5)	91 (50.3)	
GG	65 (17.8)	31 (17.1)	
A	442 (59.6)	208 (57.5)	χ^2=0.447,df=1, p=0.504
G	300 (40.4)	154 (42.5)	

Table 2: The 3 SNP haplotypes composed of rs2075507, rs4680 and rs165599 SNPs in schizophrenic patients and controls

Haplotypes	Fequency	Case, Control Ratios	Chi Square	P value
AGG	0.289	108.1:251.9, 217.0:515.0	0.016	0.8996
GAA	0.240	80.9:279.1, 181.5:550.5	0.713	0.3983
AGA	1.169	59.6:300.4, 125.3:606.7	0.051	0.8207
AAA	0.146	59.1:300.9, 100.0:632.0	1.476	0.2243
GGG	0.058	21.0:339.0, 42.4:689.6	0.0010	0.9787
GAG	0.035	15.8:344.2, 22.2:709.8	1.299	0.2544
GGA	0.032	6.3:353.7, 28.2:703.8	3.459	0.0629
AAG	0.022	9.2:350.8, 15.4:716.6	0.22	0.639

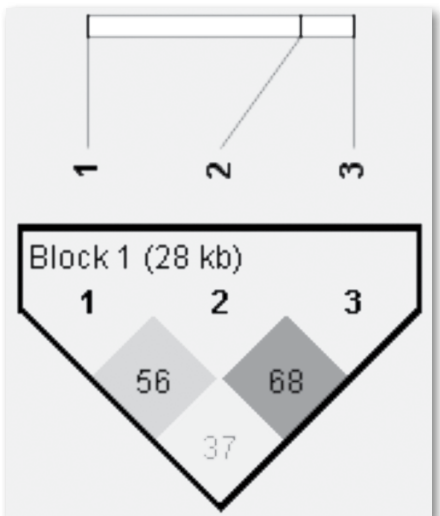

Figure 2: Linkage disequilibrium structure between any two single nucleotide polymorphisms of the COMT rs2097603, Val (108/158)Met and rs165599 is shown in the diamonds (for D').

DISCUSSION

In this present study, we did not obtain any association in the current study, between COMT rs4680 SNPs and schizophrenia in Turkish patients with schizophrenia. To date, few association studies have been performed between the COMT gene and schizophrenia in the Turkish population. One study did not obtain any association between rs4680 SNPs and schizophrenia[29], concordant with our results, but another study obtained an association between the val/val genotype and female schizophrenic patients[30]. One meta-analysis reported association between the Val allele and schizophrenia from family-based studies in European populations[7], but three other meta-

analyses did not demonstrate a significant association between rs4680 SNPs and schizophrenia in European and Asian populations[8,9,21], which is similar to our results. A recent study revealed a strong association of rs4680 and rs165774 in an Australian population[31]. But a recent meta-analysis in which a total of 51 studies comprising 13,894 patients with schizophrenia and 16,087 controls were included revealed a small but significant protective effect for heterozygosity at rs4680 in Southwestern European samples[10].

Rs2075507 and rs165599 SNPs which are in a non-coding region but effect gene expression have not previously been studied in Turkish patients with schizophrenia. The rs2075507 promoter SNPs and rs165599 functional SNPs have been associated with schizophrenia in Caucasian populations[19] and in Asian populations[20]; however, most studies have revealed a negative association between schizophrenia and these SNPs, consistent with our results[21,23,32,33].

Some reports have showed that several haplotypes rather than individual SNPs may be associated with schizophrenia due to LD differences among populations[26]. The combination of COMT rs737865, Val158Met, and rs165599 SNPs has been extensively examined for risk haplotypes for schizophrenia in earlier studies[11,14,17], but subsequent studies have revealed negative outcomes[20,32,34,35]. Funke et al.[19] revealed a potentially protective G-A-A-A haplotype of rs2075507, rs737865, rs4680 and rs165599 SNPs which was significantly under-represented in schizophrenia patients compared to controls. We have found an increase of the haplotype consisting of the G-G-A of rs2075507, rs4680, and rs165599 SNPs in controls compared to patients, but the association did not reach the level of significance. Our findings show some similarities with the work by Funke et al. For instance, we found a higher frequency of the G allele of rs2075507 and the A allele of rs165599 SNPs, but the G allele of rs4680 was found instead of the A allele in our haplotype in control individuals. Limitation of our sample size and the lack of examination of rs737865 SNPs may explain the differences in haplotype combination. It has recently been reported that an association might exist between haplotypes (G)-G-A-A [(rs4680)-rs165599-rs2075507-rs6269] and A-A-C-(G) [rs2075507-rs6269-rs4633-(rs6267)] and schizophrenia (Kong et al., 2011). Li et al. (2012) reported that the rs740603 and rs740603-(G)-rs4818(G) haplotypes were associated with negative symptoms in patients with schizophrenia, particularly among female patients among Han Chinese. However, the results of most studies were negative, similar to ours (18-20, 28, Zhang F. et al. 2012). Mukherjee et al.[22] studied DNA samples from 45 populations for 63 SNPs in a region of 172kb across the region of 22q11.2 encompassing the COMT gene. They focused on 28 SNPs spanning the COMT coding region and immediately flanking DNA, and found that the haplotypes were from diverse evolutionary lineages that could harbor as yet undetected variants with functional consequences[22].

There are various probable reasons for the discrepancies between studies. One of these could be that additional loci within COMT have an effect on gene function, ultimately effecting enzyme activity and adding complexity to the functional and clinical implications of COMT variation[13]. Cultural, life-style, environmental factors, heterology in patient groups and population differences may account for the differences in genotype and allele frequencies observed for the COMT gene. The comparison of the allele frequencies of COMT polymorphisms performed in this study showed that the frequency of the G allele of rs2075507 was 37.3%, which was similar to the frequency of 41.1% observed in the US Caucasian population[19]; however, the frequency of the G allele of rs2075507 was 26.6-28.5% in Asian populations[32,34]. Moreover, the frequency of the Met allele of rs6680 (Val108/158Met) was 43.2% in our study, which is similar to the variation of 43.3% to 52.5% observed in Caucasian and Jewish populations[14,19,23], in contrast to the frequency of 28.8%-26.6% of this allele in Asian populations[32,34]. The frequency of the G allele of rs165599 was 40.4%, which was similar to that observed in Caucasians (30.6% - 39.0%)[14,19,23]; however, the frequency of the G allele of the rs165599 was 46.6-49.2% in Asian

populations[32,34].

This study has several limitations. First, we only genotyped three polymorphisms, but the total COMT gene contains at least 50 polymorphisms. Second, schizophrenia is a heterogeneous disorder and symptom presentations vary greatly from patient to patient. Specific clinical sub-phenotypes and presumed endophenotypes of schizophrenia cannot be excluded in this study.

In conclusion, our case-control association study did not provide support for COMT rs2075507, rs4680 and rs165599 variants being associated with schizophrenia in allele/genotype and haplotype levels in a Turkish population. Further studies with larger populations in well-characterized patient populations or subgroups of patients may reveal the potential association between the COMT gene and schizophrenia.

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