Lack of Association Between COMT Gene Polymorphism and Treatment Outcome in Major Depression

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ÖZET:

KOMT gen polimorfizmi ile major depresyon tedavi sonuçları arasındak ilişki bulunmaması

Amaç: Katokolaminerjik nörotransmitter enzim yıkıcılarından Katekol-O-Metil Transferaz (KOMT)'ın anormal aktivitesi mizaç bozukluklarının patogenezinde rol oynayabilir. Bu çalışmanın amacı KOMT gen polimorfizmi ile major depresyon hastaları arasındaki ilişkiyi incelemektir.
Yöntem: Çalışma, Türk kökenli 137 majör depresyon (MD) hastası ile 153 kontrolü içermektedir. Hastalar 8 hafta süreyle antidepresan tedavisi görmüştür. Bütün hastalar Hamilton Depresyon Derecelendirme Ölçeği (HDDÖ) ile tedavi öncesi ve sonrası değerlendirilmiştir. COMT G1947A polimorfizmi PZR kökenli endonükleaz injesyon metdu ile yapılmıştır.
Bulgular: MD hastaları ile kontroller arasında anlamlı bir fark bulunamamıştır. Hasta grubunda hastalık süresi ve tedavi öncesi HDDÖ skorları ile KOMT gen polimorfizmi arasında bağıntı bulunamamıştır. KOMT genotip ve allelerinin dağılımı hasta ve controller arasında anlamlı olarak farklı değildi.
Sonuç: Bulgularımız KOMT gen polimorfizminin hasta ve controller arasında anlamlı olarak farklı olmadığını göstermiştir. MD'nin klinik görünüm ve antidepresan tedavisiyle ile ilişkili bir alel bulunamamıştır.

Anahtar sözcükler: KOMT Geni, antidepresan tedavi yanıtı, cinsiyet, major depresyon, polimorfizm

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ABSTRACT:

Lack of association between COMT gene polymorphism and treatment outcome in major depression

Background & Aim: Abnormal activity of Catechol-O-methyl transferase (COMT), as a major degrading enzyme of catecholaminergic neurotransmitters may be enrolled in the pathogenesis of mood disorders. The aim of this study was to investigate the association between COMT genetic polymorphism and major depression patients.
Method: The study included 137 unrelated major depressive disorder (MDD) patients and 153 healthy unrelated controls, all were of Turkish origin. The patients were treated with antidepressant drugs for 8 weeks. All patients were assessed by Hamilton Depression Rating Scale (HDRS) before and after the antidepressant treatment. The analysis of COMT G1947A polymorphism was performed using PCR based endonuclease digestion method.
Results: No significant difference was found between MDD and control subjects. In the MDD patients, there was no relationship between duration of illness, and pretreatment HDRS scores in respect to COMT gene polymorphism. The distribution of COMT genotypes and alleles was not significantly different among the controls and MDD patients.
Conclusion: Our findings indicated that distribution of COMT genetic polymorphism were not different significantly between the patients and controls. No allele was found to be a predictor for treatment outcome by antidepressant therapy or for clinical manifestations in MDD.

Key words: COMT gene, antidepressant treatment response, gender, major depression, polymorphism

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INTRODUCTION

Genetic factors play a significant role in determining vulnerability to mood disorders (1-3). Rapid advances in molecular genetic techniques and more precise phenotype evaluations have pointed out the possibility to identify the relationship between psychiatric disorders and genetic polymorphisms. Recent studies have been intensified on possible associations between mood disorder and candidate genes of the catecholaminergic pathway (4). On the other hand, different evidence demonstrated the interactions between serotonergic, adrenergic, and also dopaminergic system in brain (5). One of the possible candidate genes is catechol-O-methyl transferase (COMT), an enzyme that inactivates catecholamines. This enzyme catalyses the transfer of a methyl group from S-adenosylmethionine to catecholamines, resulting in one of the major degradative pathways (6,7).

There are two common variants of COMT: a low-

activity form, which is thermolabile at body temperature, and a high activity form. These differences are due to a G → A transition (NlaIII polymorphism) (8) at codon 158 of membrane-bound COMT that corresponds to codon 108 of cytoplasmic COMT (9-11). This transition causes an amino acid substitution (val-met). The COMT gene is located on the human chromosome 22 (12,13) and there is evidence from linkage studies for a susceptibility locus for depression, which also includes the COMT gene (14,15). In one sample, Ohara et al. (16) reported a positive association between variant allele of COMT that encodes the low activity enzyme and Japanese unipolar depression patients. Even though there are numerous studies about a possible association between the COMT gene and mood disorders, the results have not always been confirmed (8,11,17-19).

Although COMT is not involved in the breakdown of serotonin and is involved in noradrenergic (NA) pathways there is surprising evidence in animal studies that NA plays an important role in mediating acute behavioral and neurochemical reactions of most Selective Serotonin Reuptake Inhibitors (SSRI) (20).

In this pharmacogenetic study we aimed to investigate whether COMT gene polymorphism predisposes Turkish depressive patients to the illness as well as a possible relationship between treatment response and the polymorphism.

MATERIAL AND METHODS

The study included 166 out-patients whose ages ranged from 21 to 56 (mean, 31.48±11.3) years. None of the patients had a bipolar I or II history. All patients admitted to Department of Psychiatry at Gaziantep University School of Medicine and, 153 healthy subjects whose ages ranged from 22 to 54 (mean±SD, 30.7±6.3) years were also included in this study, and constituted the control group. They were interviewed for history of depression by asking the core symptoms (depressed mood and anhedonia) according to the DSM IV criteria by two researches and none had psychiatric history. Family history of depression was asked by the same way and none had family history of depression. The local ethical committee approved the study protocol. The participants were included in the study after giving a written informed consent.

All subjects were free of any medications at least for two weeks. Each patient underwent diagnostic evaluation by one psychiatrist on the basis of psychiatric examination to determine disorders according to DSM-IV criteria. The patients with any kind of axis I comorbidity were excluded. All subjects' sociodemographic variables were evaluated using a semistructured questionnaire form, which was arranged in accordance with the clinical experience and available information sources. Gender, age, marital status, educational condition, socio-economic status and duration of illness were noted. Additionally, the Clinician Administered Hamilton Depression Rating Scale (HDRS) (21,22) was used for rating at the beginning of the treatment and after 8 weeks. The rater was blinded to the genetic results.

Exclusion criteria were alcohol use and substance abuse or dependence, pregnancy, electroconvulsive therapy within the 6 months, presence of severe organic disorders, epilepsy or severe neurological disorder. We investigated166 unrelated outpatients suffering from major depression according to DSM-IV. The concomitant use of antihypertensive medication such as ACE inhibitors or angiotensin receptor blockers as well as hormone replacement therapies also led to exclusion from the study.

Positive response to the antidepressant treatment was defined as a 50% reduction in the total HDRS score compared with the baseline (23). Thirteen patients were excluded from the study's treatment comparison group due to their discordances with the treatment. Other clinical features such as age of onset, the number of the episode and having suicidal ideas were not evaluated within the study.

Selective serotonin reuptake inhibitors (SSRI) and Noradrenergic Specific Serotonergic Agent (NaSSA) were given to all patients and dosing was naturalistically performed. MD patients were treated with 45 sertraline (98±15mg/day), 41 citalopram (28±8mg/day), 22 Fluvoxamine (148±37mg/day), and 29 Mirtazapine (47±12mg/day).

Genotype Determination

DNA was extracted from peripheral blood leukocytes, and a PCR based restriction fragment length polymorphism assay was performed to detect the

presence of the G → A transition at position 1947 in COMT (rs4680, accession no. Z26491). PCR was used to amplify a 185 bp fragment of genomic DNA containing the polymorphism. Briefly, the primer sequences were 5'-GGAGCTGGGGGCCTACTGTG-3' (forward) and 5'-GGCCCTTTTTCCAGGTCTGACA-3' (reverse). PCR was performed in a 50 µl volume with 20-100 ng DNA, 100 µm dNTPs, 20 pmol of each primer, 1 mM MgCl2, 20 µM Tris-HCl pH 8.6, 50 µM KCl, 0.2% (w/v) bovine serum albumin and 1U Taq polymerase (MBI Fermentas).

Amplification was performed on an automated thermal cycler (Techne Genius). PCR conditions were 3 min for initial denaturation at 94°C; 35 cycles at 94°C for 1 minute for denaturation, 1 min at 60°C for annealing and 1 min at 72°C for extension, followed by 7 min at 72°C for final extension. The resulting PCR products were subjected to restriction enzyme digestion for 3 h at 37°C using 5 U NlaIII (New England BioLabs Inc.). The digest products were resolved at 100 V for 20-30 min on a 4% NuSieve 3:1 Agarose (FMC BioProducts) containing 0.5µg/ml ethidium bromide. A 100 bp marker (100 bp DNA Ladder, MBI Fermentas) was used as a size standard for each gel lane. The gel was visualized under UV light using a gel electrophoresis visualizing system (Vilber Lourmat). The COMT-HH genotype was represented by 114, 36 and 35 bp fragments; COMT-LL by 96, 36, 35 and 18 bp fragments: COMT-HL by 114, 96, 36, 35 and 18 bp fragments. The 18 bp fragment was difficult to visualize because of both its small size and co-migration with the similarly size primer residue; however, detection of this fragment was not critical in determining genotypes. Genotyping was based upon independent scoring of the results by two reviewers who were unaware of case/control status.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences for windows (SPSS) version 11.0 (SPSS, Chicago, IL). Differences in the duration of the illness, onset of age, Hamilton Depression Rating Scale scores were compared between the subjects who had different COMT genotypes using one-way analyses of variance (ANOVA). Normal distribution of the scores was assumed. Chi-square (or Fisher's exact test) was used to compare the allele and genotype frequencies between the patient and control groups. Ages were of the patients and controls were compared using t-test. The Chi-square-goodness-of-fit test was used to test the distribution of genotypes and allele frequencies for deviants from Hardy-Weinberg equilibrium. The limit of significance was set to 0.05.

RESULTS

Social and demographic parameters (age and sex) of the patients and controls were not significantly different (Table 1, p>0.05).

Allele and genotype frequencies were not significantly different between the patients and controls (χ^2=2.01, df=1, p=0.16 and χ^2=0.14, df=2, p=0.93 respectively). The COMT genotypes of the patients and controls are shown

Table 1: Demographic data of the major depressive disease (MDD) patients and control subjects. Results are expressed as mean ± standard deviation.

	MDD patients	Control
N	137	153
Age (year)	28.3±8.78	30.3±10.3
Gender (male/female)	62/75	73/80

Table 2: The distribution of different COMT genotypes and allele frequency in patients and control groups. 'N' represents the number of subjects. Expected frequencies were calculated according to Hardy-Weinberg equation. Confidence intervals ($CI_{95\%}$) are given for the for the genotypes and alleles of COMT in patients and controls.

	N	Genotype distribution [number, (%)]			Allele frequency	
		H/H (Val/Val)	H/L (Val/Met)	L/L(Met/Met)	H	L
Patients	137	51 (31%)	77 (46%)	38 (23%)	0.54	0.46
(95% CI)		(24% - 38%)	(39% - 54%)	(17% - 29%)	(0.49 - 0.59)	(0.41 - 0.51)
(expected)		48 (29%)	83 (50%)	35 (21%)		
Controls	153	50 (33%)	69 (45%)	34 (22%)	0.55	0.45
(95% CI)		(25% - 40%)	(37% - 53%)	(16% - 29%)	(0.50 - 0.61)	(0.39 - 0.50)
(expected)		47 (31%)	75 (49%)	31 (20%)		

No significant difference in genotype distribution (χ^2=0.14 df=2 p=0.93) and allele frequency (χ^2=2.01 df=1 p=0.16)

Table 3: Distribution of genotypes of COMT gene in patients with respect to treatment response

	COMT genotypes		
	H/H(Val/Val)	H/L(Val/Met)	L/L(Met/Met)
No response (n=45)	16 (%36.4)	19 (%31.1)	10 (31.3)
Response[a] (n=92)	28 (%63.6)	42 (%68.9)	22 (%68.8)
Duration of illness (month)[b]	11.2 ± 15.5	9.2 ± 9.7	14.6 ± 19.9
Pre-treatment HDRS score[c]	25.0 ± 7.7	24.5 ± 5.8	22.7 ± 5.5
Post-treatment HDRS score[d]	11.9±5.2	10.9±4.3	10.5 ± 3.7

[a]χ^2=0.255 p=0.88 Chi square test (df=2), [b]F=1.24 p=0.29 (One way ANOVA), [c]F=1.19 p=0.30 (One way ANOVA), [d]F=1.05 p=0.35 (One way ANOVA)

in Table 2. The expected frequencies of genotypes calculated according to the Hardy-Weinberg equilibrium were within the 95% confidence intervals of the observed values (Table 2).

There was no relationship between antidepressant treatment response (137 patients) and COMT variants (Table 3, χ^2=0.255, df=2, p=0.88). The onset and duration of the disease, pre- and post- treatment HDRS scores did not significantly differ depending on the genotypes of COMT.

When the patient and control groups were subdivided according to genders, There was no relationship between antidepressant treatment response and COMT variants (for males χ^2=0.69 df=2 p=0.70 and for females χ^2=0.9 df=2 p=0.63).

DISCUSSION

Relationship between allelic variation of the COMT polymorphism and antidepressant treatment seems controversial (4,24,25). An association between major depression and the genes involved in monoamine metabolism is not unexpected, given the well-known pleiotropic effects of the monoamine systems (26) and the existing evidence from the pharmacotherapy of the disease. On the other hand, Szegedi et al. (27) found association between mirtazapine treatment response and COMT polymorphism but not with paroxetine response. Benedetti et al (28) found positive effect of COMT Val (108/158) Met polymorphism on response to fluvoxamine. Arias et al (4) suggested that COMT gene could have an indirect effect of clinical response to SSRIs. Our study group had received four different antidepressants (Sertralin, Citalopram, Fluvoksamine, and Mirtazapine). Clinical response to antidepressant treatment is a complex phenomenon in which more than one neurotransmission system is probably involved. As mentioned before, NA deficiency had affected SSRI response in rats (20). In this study, we could not find an association between the functional COMT polymorphisms and antidepressant treatment efficacy. In other words, functionally different gene variants do not affect treatment outcomes in major depression. In addition, there was no relationship between COMT variants and HDRS scores and duration of the illness. A possible explanation for negative findings in our study may be sample size.

Recent pharmacogenetic studies on SSRI treatment response suggest that the antidepressant activity of fluvoxamine is related to allelic variation in tryptophan hydroxylase gene (29) as well as 5-HTT promoter (30). The same polymorphisms were also associated with differential response to paroxetine treatment in various studies (31) On the other hand, there are studies showing association between SSRIs and Serotonin Transporter Gene (32).

Small sample size, possible genotyping errors, multi-drug use and existing chronic medical illnesses other than hormone replacement and antihypertensive treated are limitations in our study. Since %15.6 of the patients were on NaSSA, this may also have influenced the results. Allele calling errors are not diminished by running internal controls.

In conclusion, according to our study, COMT gene polymorphism appeared not to predispose to depression, not to influence clinic outcome and not to change the treatment response to antidepressants.

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