Progress in Neuro-Psychopharmacology & Biological Psychiatry 36 (2012) 5–10

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Serotonin-2a receptor and catechol-*O*-methyltransferase polymorphisms in panic disorder

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ARTICLE INFO

Article history:
Received 15 May 2011
Received in revised form 11 October 2011
Accepted 12 October 2011
Available online 19 October 2011

Keywords:
Agoraphobia
Catechol-*O*-methyltransferase
Panic disorder
Polymorphism
Serotonin receptor 2A

ABSTRACT

Catechol-*O*-methyltransferase (*COMT*) and serotonin receptor 2A (*5HTR2A*) polymorphisms have been investigated for their possible role in panic disorder (PD). The aim of this study was to investigate the genotype distribution of the *COMT* val158met and *5HTR2A* 102T/C polymorphisms in PD. *COMT* val158-met is a polymorphism at codon 158 that results in variations in COMT enzymatic activity with high- (H) and low-activity (L) alleles. The *5HTR2A* 102T/C polymorphism comprises a T-to-C mutation at position 102. The effects of symptom severity, gender, and age of onset were also investigated. The participants were 105 outpatients with PD and 130 controls. The severity of the symptoms of PD was assessed by the Panic and Agoraphobia Scale (PAS). Polymorphisms of the *5HTR2A* and *COMT* genes were identified using polymerase chain reaction and restriction fragment length polymorphism analysis. A significant relationship was found between the *COMT* Val158Met polymorphism and PD. No significant differences were found in genotype distributions or allele frequencies of the *5HTR2A* polymorphisms between the PD and control groups. There were no significant relationships between the *COMT* and *5HTR2A* polymorphisms and age of onset, gender, presence of agoraphobia, or PAS scores in the PD group ($p > 0.05$).

1. Introduction

Panic disorder (PD) is a common, disabling disorder characterized by recurrent episodes of sudden and intense anxiety, accompanied by cardio-respiratory, gastrointestinal, neurological, and other autonomic symptoms and subsequent worry and phobic avoidance (Dratcu, 2000; Preter and Klein, 2008; Yeragani et al., 2000). It has a lifetime prevalence of approximately 3–5% (Grant et al., 2006; Kessler et al., 2006). It is associated with increased utilization of non-psychiatric medical services (Yamada et al., 2011), impaired quality of life (Yen et al., 2007), major depression (Biederman et al., 2004; Keller and Hanks, 1993; Rifkin and Siris, 1985), and suicide attempts (Nepon et al., 2010). Although many studies have been conducted on PD, the etiology of this debilitating disorder is still poorly understood (Hamilton, 2009). Heritability estimates for PD from twin studies are as high as 0.48, which suggests that genetic transmission plays a major role in the etiology of this disorder (Hettema et al., 2001). Although PD is believed to have a strong genetic component, the type and number of genes involved are not entirely understood.

Among the candidate genes, the Val158Met polymorphism of the catechol-*O*-methyltransferase (*COMT*) gene has been implicated in susceptibility to PD by several studies in various populations (Annerbrink et al., 2010; Domschke et al., 2004; Hamilton et al., 2002; Rothe et al., 2006). However, the impact of gender and ethnicity on the role of this genetic variation in PD remains to be assessed (Maron et al., 2010). COMT is an enzyme that inactivates catecholamines, including adrenaline, noradrenaline, and dopamine (Creveling, 2003). The *COMT* gene is located on chromosome 22q11.2. A single nucleotide polymorphism at the position of codon 158 (Val158Met) (rs4680) of the *COMT* gene results in a functional amino acid change from valine to methionine. This polymorphism is responsible for the observed high or low enzymatic activities. The valine allele (Val allele) has higher COMT

Abbreviations: PD, panic disorder; COMT, catechol-O-methyltransferase; Val, valine; Met, methionine; H, high-activity; G, guanine; L, low-activity; A, adenine; 5HTR2A, serotonin 2A receptor; 5-HT, serotonin; T, thymine; C, cytosine; PAS, panic and agoraphobia scale; DSM-IV-TR, diagnostic and statistical classification of mental disorders, fourth edition, text revision; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; ANOVA, analysis of variance; SD, standard deviation; CI, confidence interval; d.f., degrees of freedom.

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doi:10.1016/j.pnpbp.2011.10.010

activity than the methionine allele (Met allele) (Lachman et al., 1996). There is a 3- to 4-fold difference in activity between homozygotes for the high-activity (H allele: 472G, also termed the Val allele or G (guanine) allele) and low-activity (L allele: 472A, also termed the Met allele or A (adenine) allele) alleles. Heterozygotes exhibit intermediate activity (Hamilton et al., 2002).

This difference has important clinical implications; it has been suggested that individuals with the Met allele and low COMT activity have high extracellular dopamine levels and cannot cope with stressors that produce excessive dopamine (Stahl, 2008). Animal models have shown that dopamine may affect affective responses by augmenting excitatory sensory input and attenuating inhibitory prefrontal input to the amygdala (Grace and Rosenkranz, 2002) and medial striatum (Karreman and Moghaddam, 1996). A functional MRI study on healthy subjects revealed that the Met allele (A allele) was associated with a dose-dependent increase in hippocampal formation and ventrolateral prefrontal cortex activation when subjects were exposed to faces displaying negative emotions. In the same study, increased functional coupling in the limbic and prefrontal regions were found in met/met homozygotes (Drabant et al., 2006). Specifically, the Met allele (A allele) has been linked with increased levels of anxiety in women (Enoch et al., 2003), obsessive compulsive disorder in men (Karayiorgou et al., 1997), and PD (Woo et al., 2004).

The serotonin 2A receptor (*5HTR2A*) gene is located on chromosome 13q14–q21. It consists of 3 exons and 2 introns (Chen et al., 1992). The *5HTR2A* 102T/C (rs6313) polymorphism is a mutation that is defined by a T (thymine)-to-C (cytosine) transition at position 102 (Bondy et al., 1999). Because selective serotonin reuptake inhibitors are prescribed as the first-line pharmacotreatment for PD, the association of serotonin (5-HT) with the pathogenesis of PD has previously been studied (Inada et al., 2003; Judd et al., 1994; Lonsdorf et al., 2010; Pecknold and Luthe, 1990; Rothe et al., 2004; Vaswani et al., 2003). Based on these studies, two hypotheses, involving 5-HT excess or overactivity and 5-HT deficit or underactivity, have emerged. According to the 5-HT excess theory, patients with PD either have an increased level of 5-HT release or hypersensitivity of postsynaptic 5-HT receptors. On the other hand, the 5-HT deficit theory suggests that in certain brain regions such as the dorsal periaqueductal gray, 5-HT has an inhibiting effect on panic behavior; therefore, a 5-HT deficit may facilitate panic. It has also been suggested that the 5-HT system plays a dual role in modulating different forms of anxiety by inhibiting panic responses while contributing to anticipatory or generalized anxiety (Maron and Shlik, 2006).

The relationships between *COMT* (Annerbrink et al., 2010; Domschke et al., 2004, 2007, 2008; Hamilton et al., 2002; Lonsdorf et al., 2010; Ohara et al., 1998; Rothe et al., 2006; Woo et al., 2002, 2004; Zintzaras and Sakelaridis, 2007) and *5HTR2A* (Inada et al., 2003; Martínez-Barrondo et al., 2005; Rothe et al., 2004; Unschuld et al., 2007; Yoon et al., 2008) polymorphisms and PD have previously been investigated. Differing results were obtained for different ethnic groups, but these relations have not been tested in the Turkish population. The aim of this study was to assess the genotype distribution of *5HTR2A* and *COMT* polymorphisms in a Turkish population of PD patients. In addition, relationships between gender, age of onset, score on the Panic and Agoraphobia Scale (PAS), and PD were investigated.

2. Methods

2.1. Sample selection

This study was conducted according to the principles of the Declaration of Helsinki and was approved by the ethical committee of Cerrahpasa Medical Faculty Hospital. Written informed consent was obtained from the subjects after the nature of the procedures was explained. Patients were recruited from the psychiatry clinics of the same faculty hospital. Diagnosis of PD was conducted according to the Diagnostic and Statistical Classification of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria through a psychiatric interview (American Psychiatric Association, 2000). Patients with comorbid psychiatric diagnoses were excluded by the psychiatric interview, which incorporated mood, anxiety, and psychotic disorder questions based on the criteria for DSM-IV-TR. As the DSM-IV-TR implies that agoraphobia is not a codable disorder and recommends that the specific disorder with which the agoraphobia occurs should be coded, we did not consider agoraphobia a comorbid psychiatric diagnosis, but rather divided PD into PD with agoraphobia and PD without agoraphobia.

The case group included 105 unrelated patients with PD. Information about their family histories was obtained either by interviews with the person or close relatives. The age of onset was defined as the lowest age of onset reported. The control group consisted of randomly selected healthy individuals who visited the Cerrahpasa Medical Faculty Hospital for regular health screenings. Subjects were excluded if they had any self-reported personal or familial psychiatric history or psychotropic medication history. All of the participants were of Turkish origin. Ethnicity was determined by asking the participants where they were born and the language they spoke, and by directly asking them to which ethnic group they belong.

2.2. Measures

2.2.1. Panic and Agoraphobia Scale (PAS)

The severity of PD symptoms was assessed by the PAS, which is a 13-item questionnaire that covers the previous week. The PAS assesses the degree of the severity of PD by gathering information on phenomenology, frequency, and severity of panic attacks and the existence and severity of agoraphobia and phobic avoidance, anticipatory anxiety, disability, and worries about health. All of the PAS items were scored on a 5-point scale (0–4), and the total score ranged from 0 to 52 (Bandelow, 1995). A study of the reliability and validity of the PAS for the Turkish population was performed, and a cutoff score of 11 was reported by Tural et al. (2002).

2.2.2. Sociodemographic questionnaire

A sociodemographic questionnaire was developed by the investigators, consisting of items such as age and ethnicity of the participant. It also included items related to PD such as age of onset of PD and family history of PD.

2.3. Procedures

A genomic DNA sample was extracted from venous blood samples anticoagulated with EDTA. Genomic DNA was extracted from peripheral blood leukocytes with a High Pure Polymerase Chain Reaction (PCR) Template Preparation kit (Roche Diagnostics, Penzberg, Germany). Polymorphisms of the *5HTR2A* and *COMT* genes were identified using PCR and restriction fragment length polymorphism (RFLP) analysis. DNA was amplified by PCR using 20–100 ng genomic DNA, 100 μM dNTPs, 0.1 μM of each primer, 1.5 mM $MgCl_2$, 20 μM Tris–HCl (pH 8.6), 50 mM KCl, and 1 U Taq polymerase (MBI Fermentas, Vilnius, Lithuania) for *HTR2A*; and 20–100 ng genomic DNA, 100 μM dNTPs, 0.1 μM of each primer, 1 mM $MgCl_2$, 20 μM Tris–HCl (pH 8.6), 50 mM KCl, 0.2% (w/v) bovine serum albumin, and 1 U Taq polymerase in a final volume of 50 μL for *COMT*. The PCR product of the *5HTR2A* 102T/C polymorphism was digested with the *Msp*I enzyme (Warren et al., 1993). The 102T allele produces 342-bp fragments, while the 102C allele produces 126-bp and 216-bp fragments. The digested products were resolved at 120 V for 20–30 min on a 2% agarose gel containing 0.5 μg/mL ethidium bromide. The PCR product (185 bp) of the *COMT* Val158-Met polymorphism was digested with the *Nla*III enzyme (Erdal et al., 2003). The *COMT*-LL genotype produced 114-, 36-, and 35-bp

fragments; the *COMT*-HH genotype 96-, 35-, 36-, and 18-bp fragments; and the *COMT*-HL genotype 114-, 96, 36-, 35-, and 18-bp fragments. To identify the *COMT* Val158Met genotype, 4% NuSieve 3:1 agarose containing 0.5 μg/mL ethidium bromide was used. RFLP products were visualized under UV light after agarose gel electrophoresis. We used a standardized instrument for diagnosis. Techne TC-312 was used for the experimental procedure.

2.4. Statistical analysis

The data were analyzed using the statistical software SPSS for Windows (SPSS Inc., Chicago, IL). For comparison of quantitative variables, a Student's *t*-test was used for two groups and an analysis of variance (ANOVA) test was used for more than two groups. Categorical variables were compared using a Chi-square or Fisher's exact test. The significance level was $p<0.05$ and all tests were 2-tailed. G Power Analysis 3.1.2 (Universität Kiel, Germany) (Faul et al., 2007, 2009) was used for statistical power analysis. Logistic regression analysis was conducted to test the association of the polymorphisms with PD. In this analysis, the dependent variable was the case or control group, and the independent variables were age; gender; and the HH, HL, and LL genotypes for *COMT*; and TT, TC, and CC genotypes for *HTR2A*. In this analysis, we tested the odds of belonging to the PD group using one of the homozygote genotypes as a reference group for comparison with the other groups.

3. Results

The mean age of the patients in the PD group was 37.33 years and in the control group was 36.49 years; the difference was not statistically significant (Student's *t*-test, $t=0.46$, $p=0.63$). The PD group consisted of 66 female and 39 male patients and the control group consisted of 89 female and 41 male subjects, with no statistically significant difference between the groups (Chi-square test, $\chi^2=0.81$, $p=0.36$) (Table 1).

The distributions of the *COMT* and *5HTR2A* genotype and allele frequencies are presented in Tables 2 and 3, respectively. Statistically significant differences were observed in the genotype frequencies of *COMT* gene polymorphisms between the PD patients and the control group (Chi-square test, $\chi^2=8.11$, $p=0.01$). The results of the logistic regression analysis indicated that the LL genotype was significantly associated with PD ($p=0.008$) (Table 4). In addition, Chi-square analysis indicated that the statistically significant difference found in the genotype frequencies of *COMT* gene polymorphisms between the PD patients and the control group was specific to the LL genotype ($p=0.017$). The small number of HH genotype carriers compared to LL genotype carriers may have influenced these results. When the PD group was subdivided by *COMT* genotype into 3 groups (HH, HL, and LL), the 3 groups did not differ significantly in age of onset of PD (ANOVA test, $F=0.21$, $p=0.88$), gender distribution (Chi-square test, $\chi^2=1.97$, $p=0.37$), or presence of agoraphobia (Chi-square test, $\chi^2=1.51$, $p=0.46$). When the PAS scores were subdivided into high (above the cutoff point = scores of ≥11) and low (below the cutoff = scores <11), there were no significant differences among the 3 *COMT* genotype groups in their PAS scores (Chi-square test, $\chi^2=1.79$, $p=0.40$).

The *5HTR2A* polymorphisms were found not to be associated with PD in the logistic regression analysis ($p>0.05$) (Table 4). Likewise, Chi-square analysis found that there were no significant differences in the genotype distributions or allele frequencies of the *5HTR2A* polymorphisms between the PD and control groups (Chi-square test, $\chi^2=3.16$, $p=0.20$). When the PD group was subdivided by *5HTR2A* genotype into 3 groups (TT, TC, and CC), the 3 groups did not differ significantly in age of onset of PD (ANOVA test, $F=0.85$, $p=0.42$), gender distribution (Chi-square test, $\chi^2=0.31$, $p=0.85$), or presence of agoraphobia (Chi-square test, $\chi^2=3.07$, $p=0.21$). When the PAS scores were subdivided into low and high, there were no significant differences among the 3 *5HTR2A* genotype groups in their PAS scores (Chi-square test, $\chi^2=1.79$, $p=0.40$).

A sub-analysis for associations across patients and controls stratified for gender identified that the HL genotype of *COMT* was significantly more prevalent in female patients (Chi-square test, $\chi^2=12.110$, $p=0.002$). There were no significant differences for males (Chi-square test, $\chi^2=0.027$, $p=0.987$). For the *HTR2A* genotype, no differences were found between the case and control groups for females (Chi-square test, $\chi^2=4.007$, $p=0.135$) or males (Chi-square test, $\chi^2=2.606$, $p=0.272$).

When the statistical power was analyzed using G Power Analysis, with an expected size of 105 patients and 130 controls and an effect size of 0.26 for the *COMT* genotype (the mutation rate was 0.33 for the case group and 0.21 for the control group), the calculated power

Table 1
General characteristics of panic disorder patients and controls.

Participants	Sex (M/F)	Age (years, mean ± SD)	Age of onset (years, mean ± SD)	Family history of PD (*n*)
Patients with PD ($n=105$)	39/66	37.33 ± 11.48	28.93 ± 6.36	15
With agoraphobia ($n=34$)	10/24	33.68 ± 13.19	25.76 ± 7.18	9
Without agoraphobia ($n=71$)	29/42	39.09 ± 10.02	30.45 ± 7.28	6
Control subjects ($n=130$)	41/89	36.49 ± 15.95		

F, female; M, male; PD, panic disorder; SD, standard deviation.

Table 2
Distributions of *COMT* genotype and allele frequencies.

COMT gene	PD patients	Control group	*p*
HH *n* (%)	19 (18.1%)	16 (12.3%)	0.017
HL *n* (%)	51 (48.6%)	87 (66.9%)	$\chi^2=8.11$
LL *n* (%)	35 (33.3%)	27 (20.8%)	
H allele frequency	42.4	45.8	0.46
L allele frequency	57.6	54.2	$\chi^2=0.54$

COMT, catechol-*O*-methyltransferase; PD, panic disorder.

Table 3
Distributions of *5HTR2A* genotype and allele frequencies.

5HTR2A gene	PD patients	Control group	*p*
T/T *n* (%)	29 (27.6%)	32 (24.6%)	0.20
T/C *n* (%)	53 (50.5%)	56 (43.1%)	$\chi^2=3.16$
C/C *n* (%)	23 (21.9%)	42 (32.3%)	
T allele frequency	52.9	46.2	0.15
C allele frequency	47.1	53.8	$\chi^2=2.09$

5HTR2A, serotonin 2A receptor; PD, panic disorder.

Table 4
Association of the *COMT* and *5HTR2A* polymorphisms with PD.

Polymorphism	PD patients	Control group	*p*	Odds ratio (95% CI)
COMT HH	19 (18.1%)	16 (12.3%)	0.055	2.093
COMT HL + LL	86 (81.9%)	114 (87.7%)		(0.984–4.451)
COMT LL	35 (33.3%)	27 (20.8%)	0.008	2.294
COMT HL + HH	70 (66.7%)	103 (79.2%)		(1.240–4.244)
5HTR2A TT	29 (27.6%)	32 (24.6%)	0.424	1.275
5HTR2A TC + CC	76 (72.4%)	98 (75.4%)		(0.703–2.312)
5HTR2A CC	23 (21.9%)	42 (32.3%)	0.92	0.762
5HTR2A TC + TT	82 (78.1%)	88 (67.7%)		(0.555–1.046)

Age and gender were controlled for in the logistic regression analyses. *COMT*, catechol-*O*-methyltransferase; *5HTR2A*, serotonin 2A receptor; PD, panic disorder.

Table 5
Interactions between the *HTR2A* and *COMT* polymorphisms in predicting the Panic Agoraphobia Scale.

Variable	*F*	*p*	Partial Eta Squared	d.f.
HTR2A	0.198	0.821	0.004	2
COMT	0.452	0.638	0.010	2
*HTR2A*COMT*	0.258	0.904	0.011	4
Age	0.045	0.832	0.000	1
Sex	0.714	0.400	0.008	1

d.f., degrees of freedom; $r^2 = 0.827$. Dependent variable: Panic Agoraphobia Scale.

was 0.75 with a confidence interval (CI) of 95%. Power analysis for the *5HTR2A* genotype determined a power of 0.59 with an effect size of 0.21 (the mutation rate was 0.22 for the case group and 0.32 for the control group).

Interactions between the *HTR2A* and *COMT* polymorphisms were tested by covariance analysis with PAS as the dependent variable. There were no significant interactions between the *HTR2A* and *COMT* polymorphisms ($p = 0.874$) (Table 5).

Agoraphobia was found in 41 of the patients with PD; 37% of the female patients and 26.2% of the male patients had agoraphobia, but the difference was not statistically significant (Chi-square test, $\chi^2 = 1.28$, $p = 0.25$). Patients with agoraphobia had a significantly earlier onset of PD (mean age of onset $= 25.76 \pm 7.18$) than did patients without agoraphobia (mean age of onset $= 30.45 \pm 7.28$) (Student's *t* test, $t = 3.09$, $p = 0.003$). When the age of the participants was controlled for in the covariance analysis, the significance dropped to $p = 0.047$.

The PAS scores used to assess the severity of PD had a mean of 23.17 ± 10.97. When the PAS scores were subdivided into high (≥ 11) and low (<11) groups, these two groups did not differ in terms of gender (Chi-square test, $\chi^2 = 1.35$, $p = 0.50$), and PAS scores did not differ between males and females (Chi-square test, $\chi^2 = 2.95$, $p = 0.08$). Patients with agoraphobia had higher PAS scores (Chi-square test, $\chi^2 = 5.87$, $p = 0.01$).

4. Discussion

In the present study, we investigated the association between PD and the *COMT* val158met and *5HTR2A* 102T/C polymorphisms in a Turkish population. A significant relationship was found between the LL genotype of the *COMT* Val158Met polymorphism and PD. No significant differences were found in the genotype distributions or allele frequencies of the *5HTR2A* polymorphism between the PD and control groups.

The *COMT* Val158Met polymorphism has been identified as having an association with several anxiety disorders, with PD demonstrating the most consistent results in a number of studies (Annerbrink et al., 2010; Hamilton et al., 2002; Hettema et al., 2008; Rothe et al., 2006). On the other hand, this association was not found in other studies (Ohara et al., 1998). We found that the LL genotype was significantly associated with PD. This result is consistent with two previous studies involving East Asian patients (Woo et al., 2002, 2004).

Our findings were consistent with previous reports (Stahl, 2008) suggesting that valine carriers at codon 158 of the *COMT* gene with high COMT activity can cope with excess dopamine under stress and are not worried or afraid. Stahl (2008) concluded that individuals with the methionine genotype and low COMT activity have high dopamine levels, and thus they decompensate when stressors produce excessive dopamine levels, disrupting cognitive information processing and generating symptoms of anxiety. Our study confirms this relationship between low COMT activity and the development of anxiety in the form of panic attacks. This finding contributes to our understanding of how atypical antipsychotics alleviate the symptoms of anxiety. Atypical antipsychotics such as risperidone are known to alleviate anxiety symptoms through direct modulation of the dopamine system and are effective in treating PD (Stahl, 2008). Polymorphisms of *COMT* may be a determinant of treatment response, in that carriers of the L allele (Met allele or A allele) have higher dopamine levels and would be more responsive to treatment with antipsychotics. In our study, we did not assess treatment response; this relationship may be addressed in future studies.

Our findings were inconsistent with some previous studies that have found a significant association between the Val allele of *COMT* (H allele or G allele) with PD, especially in women (Domschke et al., 2004; Hamilton et al., 2002; Hettema et al., 2008; Ohara et al., 1998; Rothe et al., 2006). We did not find a gender-specific effect in relation to the *COMT* polymorphisms in the case group, but when we conducted a subanalysis for associations across patients and controls stratified for gender, we found that the *COMT* genotype was significantly more prevalent in female patients.

Two meta-analyses have been performed to clarify the relationship between PD and *COMT* polymorphisms. A meta-analysis conducted by Domschke et al. (2007) indicated that studies of Caucasian samples (Hamilton et al., 2002; Rothe et al., 2006) revealed a significant association between the *COMT* 158 Val allele (L allele or G allele) and PD, whereas there was a trend toward association of the *COMT* 158 Met allele with PD in Asian samples. The results of our sample, which was composed of Turkish individuals, are not consistent with most findings for Caucasian samples (Hamilton et al., 2002; Rothe et al., 2006), but are similar to those for Asian samples (Woo et al., 2002, 2004). One of the factors that may account for discrepancies between our study and that of the other Caucasian samples is the ethnic composition of Turkey, which includes both Asian and European individuals. In the other meta-analysis, the same studies were analyzed, and no conclusive evidence was found showing that the 472G/A polymorphism was a reliable marker for PD (Zintzaras and Sakelaridis, 2007). Therefore, large differences in interpretation exist between the two meta-analyses.

In our study, we found no significant statistical differences in the genotype distributions or allele frequencies of the *5HTR2A* polymorphisms between the PD and control groups. Consistent with our findings, the studies of Fehr et al. (2001), Martínez-Barrondo et al. (2005), and Rothe et al. (2004) found no association between *5HTR2A* gene polymorphisms and PD in German and Canadian patients. In Rothe et al. (2004), the role of the *5HTR2A* 102T/C polymorphism in PD was not supported in a combined Canadian and German sample of patients. In their study, comorbidity with other anxiety and mood disorders was allowed; this distinguishes their study from ours, which included only patients without any psychiatric comorbidities.

In contrast to our findings, some studies (Inada et al., 2003; Maron et al., 2005) have reported that the *5HTR2A* 102T/C polymorphism was associated with PD. Inada et al. (2003) reported a significant association with a *5HTR2A* silent 102T/C polymorphism in PD patients with a pure phenotype, and particularly with agoraphobia. Maron et al. (2005) also showed a significant association with the *5HTR2A* 102T/C polymorphism in pure, but not in comorbid PD. Both studies reported that the 102C allele was more frequent among PD patients, suggesting a significant role for this allele in predisposition to PD. There may be a number of reasons for this inconsistency. First, the ethnic composition of the previous studies, which were Japanese (Inada et al., 2003) and Estonian (Maron et al., 2005), may play a role. On the other hand, no evidence was found for this association in a study analyzing another Estonian sample (Martínez-Barrondo et al., 2005). Thus, there may be other factors contributing to this discrepancy such as sample size and the inclusion criteria used in the sample selection process.

Our study has several limitations which should be kept in mind when the findings are interpreted. First, as this was not a birth cohort study, the age of onset was reported by the patients and may be subject

to recall bias. Second, as patients were not followed up and the response to treatment was not recorded, the impact of these polymorphisms on treatment could not be assessed. Third, the relatively small sample size may have contributed to the low power (0.59) for the *5HTR2A* genotype. Future studies with larger sample sizes may shed light on the association between the *5HTR2A* polymorphism and PD.

5. Conclusion

In conclusion, we found that the *COMT* Val158Met polymorphism was significantly associated with PD in a Turkish population of PD patients. This difference in the frequency of polymorphisms between patient and control groups was specific to the LL genotype. The *5HTR2A* polymorphism was not associated with PD in our study population. The HL *COMT* genotype was significantly more prevalent in female patients, whereas no differences were found for males.

Acknowledgments

The preliminary findings of this study were presented at the 8th Balkan Meeting on Human Genetics, May 14–17, 2009, Cavtat-Dubrovnik, Croatia, and at the 11th National Medical Biology and Genetics Congress, October 28–31, 2009, Bodrum, Turkey. This study was supported by the University of Istanbul Scientific Research Projects Unit (project number: 2060).

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