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Cathecol-O-methyl transferase Val158Met genotype is not a risk factor for conversion disorder

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ABSTRACT. Alterations in catechol-O-methyltransferase (COMT) activity are involved in various types of neurological disorders. We examined a possible association between the COMT Val158Met polymorphism and conversion disorder in a study of 48 patients with conversion disorder and 48 control patients. In the conversion disorder group, 31 patients were Val/Met heterozygotes, 15 patients were Val/Val homozygotes and 2 patients were Met/Met homozygotes. In the control group, 32 patients were Val/Met heterozygotes and 16 patients were Val/Val homozygotes. There was no significant difference between the groups. We conclude that the COMT Val158Met genotype is quite common in Turkey and that it is not a risk factor for conversion disorder in the Turkish population.

Key words: COMT; Val158Met genotype; Conversion disorder

INTRODUCTION

The enzyme catechol-O-methyltransferase (COMT) catabolizes catecholamine neurotransmitters including dopamine in the central nervous system. Allelic variation in the COMT gene is thought to influence dopamine regulation in prefrontal regions of the brain. Lachman et al. (1996) first reported a common biallelic single nucleotide polymorphism (SNP) at codon 158, which involved a substitution of valine (Val) for methionine (Met), in the gene coding for COMT. This SNP at codon 158 in the COMT gene has been found to affect the thermostability of the COMT enzyme. Thus, the Met allele of this polymorphism has been associated with a 2- to 4-fold reduction in COMT enzyme activity (Lotta et al., 1995; Weinshilboum et al., 1999; Chen et al., 2004). Owing to the relative shortage of dopamine transporters in the human prefrontal cortex, COMT is believed to have a particularly important role in regulating levels of dopamine there (Lewis et al., 2001; Tunbridge et al., 2004). Consequently, a reduction in COMT activity, conferred by the Met allele inheritance, may increase dopamine availability in the prefrontal cortex, and the Val allele may increase COMT activity related to reduced dopamine availability (Chen et al., 2004; Tunbridge et al., 2004).

In both adult human and animal studies, COMT activity and the dopaminergic system have been associated with various psychiatric disorders. Numerous studies have investigated the relationship between the COMT Val/Met polymorphism at codon 158 (Val158Met) and behavioral phenotypes and various psychiatric disorders. The COMT Val158Met genotype is a risk factor for schizophrenia, bipolar disorder, obsessive-compulsive disorder, aggressive behavior, and attention problems. The functional COMT Val158Met polymorphism has been thoroughly investigated in several psychiatric disorders, and a relationship seems to be present between dopaminergic activity and psychiatric disorders (Craddock et al., 2006).

Conversion disorder is a common cause of referrals to emergency services. It is a mental disorder characterized by symptoms that suggest a neurologic or general medical condition but that cannot be fully explained by a neurologic or mental disorder diagnosis. Conversion disorder is one of several somatoform disorders (conversion disorder, hypochondriasis, somatization disorder, somatoform pain disorder) characterized by persistent physical symptoms for which no cause can be found.

Conversion disorder is much more frequent in women. The most common ages of presentation are adolescence or early childhood, but patients in other age groups may be affected (Sadock and Sadock, 2000). Conversion disorders are more prevalent in rural, poorer, and less-educated populations. Other predisposing factors include medical illness, depression, anxiety, schizophrenia, somatization disorder, dependent personality disorder (5 to 21% of patients), borderline personality disorder, and passive aggressive personality disorder (Binzer et al., 1997; Sadock and Sadock, 2000).

Conversion disorder usually presents as a single symptom with a sudden onset related to severe stress. The presentation may vary in recurrences (Dula and DeNaples, 1995; Binzer et al., 1997; Sadock and Sadock, 2000). Classic symptoms of conversion disorder include paralysis, aphonia, seizures, coordination disturbances, akinesia, dyskinesia, blindness, tunnel vision, anosmia, anesthesia, and paresthesia (Stonnington et al., 2006). The diagnosis is made primarily by ruling out organic pathology. The absence of a medical condition does not necessarily support the diagnosis of conversion disorder; however, because appropriate psychological criteria also must be met. Relevant laboratory and ancillary studies should be ordered to confirm suspected organic disease (Purcell, 1991).

In the present study, we tested a hypothesis regarding the relationship between the Val158Met genotype (Val homozygotes *vs* Met carriers) and conversion disorder. Previously, many studies of the COMT enzyme in various psychiatric disorders have been carried out, but no studies to date have examined the relationship between conversion disorder and the COMT Val158Met genotype.

MATERIAL AND METHODS

Subjects

The study was performed in 2011. Patients with conversion disorder diagnoses who voluntarily participated in the study were admitted to the Emergency Department of Uludag University for a conversion reaction or another reason. The diagnosis of conversion disorder was made using the following criteria:

1) the patient complains of a change or loss of physical function suggesting a physical disorder,

2) the patient has experienced a recent psychological stressor or conflict,

3) the patient unconsciously produces the symptom,

4) the symptom cannot be explained by a known organic etiology or culturally sanctioned response pattern, and

5) the symptom is not limited to pain or sexual dysfunction (American Psychiatric Association, 2000).

All patients with conversion disorder diagnoses were evaluated to rule out organic pathologies and referred to psychiatry. A control group established from voluntary patients without known psychiatric illness who were admitted to the Emergency Department for another reason. Forty-eight patients with conversion disorder and 48 controls participated in the study. The study was approved by the Uludag University Ethics Committee.

DNA extraction and COMT genotyping

DNA was extracted in the Emergency Department from blood samples taken from each participant in the 2 groups. All DNA extractions and genotyping were performed in the Department of Genetics at Uludag University.

Blood samples were drawn into tubes containing ethylenediaminetetraacetic acid. DNA isolation was performed using a genomic DNA purification kit according to manufacturer instructions, and samples were stored at -20°C until needed for polymerase chain reaction (PCR).

The COMT gene Val158Met polymorphism was determined using the PCR-restriction fragment length polymorphism method. For the mannose-binding lectin (MBL) gene codon 54 polymorphism, forward 5'-CTCATCACCATCGAGATCAA-3' and reverse 5'-CCAGGTCTG ACAACGGGTCA-3' primers were used (Albaugh et al., 2010). PCR primers for Val158Met were used to generate a 109-bp PCR product containing the polymorphic sites. PCR products were digested overnight with *Nla*III at 37°C and analyzed on 4% agarose gels. The fragments used to discriminate each genotype were as follows: Val homozygotes (86 and 23 bp), Val/Met heterozygotes (86, 68, 23, and 18 bp), and Met homozygotes (68 and 18 bp).

Statistical analysis

Data are reported as means ± standard deviation. A chi-square test was used to compare genotype and allele frequencies. P values smaller than 0.05 were accepted as statistically significant.

RESULTS

The conversion disorder group comprised 33 women and 15 men; the control group contained 32 women and 16 men. The median age for the conversion group was 22.50 (min. = 15; max. = 80). In the control group, the median age was 23 (min. = 10; max. = 70). No significant difference was found between the groups with respect to gender (P = 0.758) or age (P = 0.06).

In the conversion disorder group (N = 48), 15 patients were Val/Val homozygotes, 31 patients were Val/Met heterozygotes, and 2 patients were Met/Met homozygotes. In the control group (N = 48), 16 patients were Val/Val homozygotes and 32 patients were Val/Met heterozygotes. We compared each genotype statistically within the groups. No significant differences were found in the comparison of Val homozygotes and Met carriers. Genotype frequencies of COMT polymorphisms in patients and controls are shown in Table 1.

Table 1. Genotype frequencies of catechol-O-methyltransferase polymorphisms in patients and controls.

Variables	Patients (N = 48)	Controls (N = 48)	P
Genotypes			
Val/Val	15	16	0.119
Val/Met	31	32	0.70
Met/Met	2	0	0.121
Frequency of allele			
Val (%)	64	67	0.65
Met (%)	36	33	0.65

DISCUSSION

The primary aim of the present study was to test the association between Val158Met genotype and conversion disorder. We hypothesized that a relationship might exist between Val158Met polymorphisms and conversion disorder. To our knowledge, no study has examined this relationship.

In both adult human and animal studies, COMT activity and the dopaminergic system have been associated with various psychiatric disorders. COMT knockout mice with higher levels of extracellular dopamine have been reported to exhibit heightened aggression, but Gogos et al. (1998) have emphasized that this result was found only in male mice. The role of the Val158Met polymorphism is still unclear, but some recent studies have reported associations between the Val allele and increased aggression (Caspi et al., 2008; Monuteaux et al., 2009). Numerous studies have investigated the relationship between the Val158Met polymorphism and behavioral phenotypes and various psychiatric disorders. The COMT Val158Met genotype has been reported as a risk factor for schizophrenia, bipolar disorder, obsessive-compulsive disorder, aggressive behavior, and attention problems, although some studies conclude the opposite (Eisenberg et al., 1999; Kereszturi et al., 2008; Sengupta et al., 2008). The functional

COMT Val158Met polymorphism has been thoroughly investigated in several psychiatric disorders (Craddock et al., 2006). A few studies are available on bipolar disorder, and their results are inconclusive (Gutierrez et al., 1997; Kunugi et al., 1997; Shifman et al., 2004).

The COMT Val158Met polymorphism has also been implicated in attention problems, including symptoms of attention deficit/hyperactivity disorder (ADHD). Past studies have revealed associations between the Val allele and forms of distractibility and "off-task" behavior (Sengupta et al., 2008; Holmboe et al., 2010). Others have reported an association between the Val allele and ADHD (Eisenberg et al., 1999; Kereszturi et al., 2008). Some groups, have found associations between the Met allele and increased ADHD symptom count or severity in young subjects (DeYoung et al., 2010; Palmason et al., 2010).

Numerous studies have investigated the relationship between the Val158Met polymorphism and various psychiatric disorders. The COMT Val158Met genotype is thought to be a risk factor for schizophrenia, bipolar disorder, obsessive-compulsive disorder, aggressive behavior, and attention problems; however, there are some studies that advocate the opposite (Eisenberg et al., 1999; Sengupta et al., 2008; Kereszturi et al., 2008).

Monuteaux et al. (2009) replicated evidence that the COMT Val158Met is associated with phenotypic variation among children with ADHD. Albaugh et al. (2010) argued that a strong association exists between youth carrying a Met allele and higher than average aggression scores in ADHD patients compared with those in Val homozygotes. Wirgenes et al. (2010) replicated data suggesting an association between the Val158Met variant and working memory performance and found a significant interaction between this SNP and schizophrenia. Shifman et al. (2004) reported a significant association between a COMT haplotype and schizophrenia. They also found a significant association between bipolar disorder and COMT polymorphisms.

Gutierrez et al. (1997) studied the frequency of the C256 allele and Val108 variant but found no allelic or genotypic association, which they interpreted to mean that the COMT gene is not a major risk factor for bipolar disorder. Kunugi et al. (1997) stated the outcome of their study in its title: "No evidence for an association of affective disorders with high- or low-activity allele of catechol-o-methyltransferase gene". Glatt et al. (2003) concluded that the Val allele may be a small but reliable risk factor for schizophrenia in people of European ancestry, but the influence of this polymorphism on risk in Asian populations remains unclear.

Our study found no association between conversion disorder and the COMT Val158Met genotype, but did determine that the COMT Val158Met genotype is quite common among healthy subjects. No relationship existed between the COMT Val158Met genotype and conversion disorder in the sampled Turkish population. Further investigations should be carried out in various population groups to confirm these results.

Our study is important given that no similar studies about conversion disorder are available. Additional research is needed to obtain more detailed insight about genetic risk factors and conversion disorder. Because, like other psychiatric disorders, conversion disorder may be associated with genetic predispositions, additional genetic risk factors should be considered and investigated.

The COMT Val158Met genotype is not a risk factor for conversion disorder for the Turkish population. Our study found that the COMT Val158Met genotype is quite common among normal subjects. Other genetic risk factors may be associated with conversion disorder, and further investigation of these factors should be carried out in various population groups.

Conflicts of interest

The authors declare no conflicts of interest.

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