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Catechol-*O*-methyltransferase Val108/158Met gene and alcoholism in Turkish subjects

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Aim: To determine if the functional Val108/158Met polymorphism causes a tendency toward alcohol addiction in Turkish cases. This polymorphism of the catechol-O-methyltransferase (COMT) gene has been associated with many psychiatric disorders, as well as with alcoholism.

Materials and methods: The allele and genotype associations of the Val108/158Met polymorphism in 110 Turkish alcoholics and 330 healthy subjects were investigated, constituting our study and control groups, by polymerase chain reaction-restriction fragment length polymorphism.

Results: Distribution of the Met/Met genotype was 16.4% to 20.6% and frequency of the Met allele was 36.8% to 39.5% in the study group compared to the control group. The results did not show any significant differences in the genotype distribution and allele frequencies of the polymorphism, neither between the study and the control groups ($c^2 = 0.985$, $P = 0.611$ and $c^2 = 0.517$, $P = 0.472$) nor between female ($c^2 = 0.247$, $P = 0.884$ and $c^2 = 0.115$, $P = 0.735$, respectively) and male ($c^2 = 0.728$, $P = 0.695$ and $c^2 = 0.485$, $P = 0.486$, respectively) alcoholics. The power of the study for genotype analysis was set at 79.1%.

Conclusion: The present study shows that the polymorphic Met allele of the COMT polymorphism is not associated with alcoholism in Turkish cases; however, due to the lack of statistical power, this research should be evaluated again with an enlarged study group to confirm the possible association between the polymorphism and alcoholism.

Key words: Alcoholism, catechol-O-methyltransferase, COMT Val108/158Met, polymorphism

Türk olgularda katekol-*O*-metiltransferaz Val108/158Met gen polimorfizmi ve alkolizm

Amaç: Fonksiyonel Val108/158Met polimorfizminin Türk olgularda alkol bağımlılığına yatkınlık sağlayıp sağlamadığını belirlemek. Katekol-O-metiltransferaz (COMT) geninin bu polimorfizmi, alkolizm de dahil olmak üzere pek çok psikiyatrik hastalık ile ilişkilendirilmiştir.

Yöntem ve gereç: Çalışma ve kontrol gruplarını oluşturan 110 Türk alkol bağımlısı olgu ve 330 sağlıklı bireyde, Val108/158Met polimorfizminin genotip ve alel ilişkisi PCR-RFLP yöntemiyle incelenmiştir.

Bulgular: Çalışma grubu kontrol grubuyla kıyaslandığında; Met/Met genotipinin dağılımı % 16,4' e % 20,6 iken, Met alelinin sıklığı % 36,8' e % 39,5 olarak bulunmuştur. Sonuçlarımıza göre, genotip dağılımı ve alel sıklığı açısından çalışma ve kontrol grupları arasında ($c^2 = 0,985$, $P = 0,611$ ve $c^2 = 0,517$, $P = 0,472$) ve alkol bağımlısı kadın ($c^2 = 0,247$, $P = 0,884$ ve $c^2 = 0,115$, $P = 0,735$ sırasıyla) alkol bağımlısı erkek ($c^2 = 0,728$, $P = 0,695$ ve $c^2 = 0,485$, $P = 0,486$ sırasıyla) arasında anlamlı bir fark saptanmamıştır. Çalışmanın gücü genotip analizi açısından % 79,1 olarak hesaplanmıştır.

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Sonuç: Bu çalışma her ne kadar COMT geni polimorfik Met alelinin Türk olgularda alkolizmle ilişkisi olmadığını göstersede; istatistiki güç analizinin düşük olması nedeniyle araştırma daha geniş bir çalışma grubuyla tekrar değerlendirilmelidir böylelikle alkolizm ile polimorfizm arasındaki olası asosiasyon doğrulanabilecektir.

Anahtar sözcükler: Alkolizm, katekol-O-metiltransferaz, COMT Val108/158Met, polimorfizm

Introduction

Alcohol addiction or alcoholism is a multifactorial disease with genetic and environmental factors involved in its etiology. The genetic factors playing a role in the development of alcoholism have been reported from family, twin, and child adaptation studies, and molecular studies (1,2). Although the mechanisms of the genetic transmissions and its pathophysiology have not been completely understood and solved, it is certain that many neurotransmitter systems play a role in the pathophysiology of alcoholism (3). For alcohol-seeking behavior, it has been shown that the synthesis and metabolism of dopamine in the mesolimbic/mesocortical awarding system of the brain and the amount of active dopamine receptors have an important impact on ethanol-reinforced responding (4). The psychological calming effects of alcohol are achieved by the rapid dopamine release from the brain's limbic system after alcohol consumption (3). Consequently, changes in the enzymes involved in the synthesis and metabolism of dopamine, and components of the receptor systems, have been the focus of investigations of addiction.

The catechol-*O*-methyltransferase (COMT) enzyme plays an important role in the inactivation of epinephrine and norepinephrine, and also in the inactivation of dopamine (5). In a common functional polymorphism of the COMT gene, a valine amino acid at codon 108/158 is changed to methionine, which results in a 3- to 4-fold loss of enzyme activity (6-8). In relation to alcoholism, it is known that individuals with a low-activity COMT variant metabolize high amounts of dopamine, which is rapidly released from the limbic region after alcohol consumption, more slowly than individuals with a high-activity COMT variant, and are therefore more exposed to the pleasurable effects of dopamine (5). This mechanism might account for the predisposition of some individuals to alcohol abuse.

This common and functional Val108/158Met COMT polymorphism has been investigated in relationship with many disorders, like velocardiofacial syndrome (9), rapid cycling bipolar disorder (10,11), schizoaffective and schizophrenic disorders (7,12), and obsessive-compulsive disorder (13). In these studies, an association, and also a lack of association, between the COMT Val108/158Met polymorphism and the studied psychiatric disorders were found.

In studies in which the relationship between the COMT Val108/158Met polymorphism and alcoholism was analyzed, different results were obtained according to differences in the included study groups. In some studies, no association between the COMT Val108/158Met polymorphism and alcoholism was found (2,14,15). In a study where the weekly alcohol consumption of social male drinkers was investigated in association with the COMT Val108/158Met polymorphism, it was shown that individuals carrying the COMT genotype responsible for low enzyme activity consumed more alcohol during the week (16). Type 1 alcoholism, which is more frequently observed in the population and starts after the age of 25 without antisocial behavior, has also been associated with the COMT genotype responsible for low enzyme activity (5,17). However, for type 2 alcoholism, which is less frequently observed in the population, starts before the age of 25, and is usually accompanied with antisocial behavior, contradictory results have been obtained related to the association between the COMT genotype, responsible for low enzyme activity, and alcoholism (2,17-19). Since there is still much controversy over the studies investigating the association of the COMT Val108/158Met gene polymorphism with alcoholism, this study aimed to address this issue further with Turkish alcoholics and to investigate whether sex and ethnic differences might play a role in the association between the COMT Val108/158Met gene polymorphism and alcoholism.

Materials and methods

The study group included 110 unrelated subjects (100 men, 46 ± 9.28 years, and 10 women, 36 ± 7.77 years) who were assessed by a structured clinical interview (SCID) for Axis I of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association, 1994) by a psychiatrist; all of the subjects met the DSM-IV diagnostic criteria for alcohol dependence and none had comorbid psychiatric disorders. All subjects were chosen from among 680 people who applied to the Ege University Medical Faculty Psychiatry Department's Addiction Center from the Aegean region of Turkey between 2005 and 2010, and who interviewed with a psychiatrist for the cure of alcoholism. Alcohol consumption severity was assessed through 22 questions from the Michigan Alcohol Screening Test (MAST). The MAST is widely used in order to determine alcohol abuse disorders (20). Sociodemographic data (age, marital status, and level of education) and previous personal and familial psychiatric history, personal drug use (including nicotine), and legal problems were recorded.

The control group consisted of 330 unrelated healthy subjects (229 men, 44.51 ± 14.23 years, and 101 women, 36 ± 7.45 years). All of the control group subjects were selected from the same Aegean region of Turkey as the study group subjects, and they were evaluated as physically and mentally healthy by a psychiatrist according to the SCID nonpatient form.

The study design adhered to the Declaration of Helsinki and was approved by the Ege University Medical Faculty Ethical Committee prior to the study's initiation. Signed consent forms were collected from all of the study participants. No relationship existed between any of the subjects in the study and the control groups.

Genotype analysis of the COMT Val108/158Met polymorphism (rs 4680)

From each of the 440 participants, 3 mL of peripheral venous blood was collected into tubes containing ethylenediaminetetraacetic acid (EDTA), and genomic DNA was isolated according to the protocols of the High Pure PCR Template Preparation Kit (Roche Applied Science, Germany). A 203-bp fragment of the COMT gene harboring the polymorphic site of interest was amplified using the following primer pair: forward 5'-CTCATCACCATCGAGATCAA-3' and reverse 5'-GATGACCCTGGTGATAGTGG-3'. The polymerase chain reaction (PCR) reaction mix contained 25 mM $MgCl_2$, 100 μM of each primer, 2 mM dNTP mix, 10× PCR buffer, 1 U Taq DNA polymerase, and 50 nmol of genomic DNA. The PCR conditions were set as 1 min of initial denaturation at 94 °C followed by 40 cycles of 20 s of denaturation at 94 °C, 30 s of annealing at 56 °C and 30 s of elongation at 72 °C, and a final extension of 7 min at 72 °C. The resulting PCR product was purified from the undesired small side products (<100 bp) using the High Pure PCR Product Purification Kit. From the purified PCR product, 10 μL was digested with 1 U *Nla*III (*Hin1II*, Fermentas) for 4 h at 37 °C and analyzed after running on a 12% polyacrylamide gel (29:1) stained with ethidium bromide (EtBr). The presence of guanine nucleotide at codon 108/158 (GTG/Val/high COMT enzyme activity) resulted in 3 fragments of 87 bp, 62 bp, and 54 bp after digestion. However, when an adenine nucleotide was present at the same codon instead (ATG/Met/low COMT enzyme activity), 4 fragments of 69 bp, 62 bp, 54 bp, and 18 bp were observed. The results were duplicated by studying the same samples with an electrochemical biosensor system described elsewhere (21).

Statistical analysis

Allele and genotype frequencies were compared among the study and control subjects using the chi-square and ANOVA tests. $P < 0.05$ was considered statistically significant and the results were evaluated with SPSS 11.0 for Windows. Power analysis of the genotype distribution was performed with the NCSS-PASS 2000 program; the power calculated for α was set at 0.05. The study group subjects were consistent with the Hardy-Weinberg equilibrium ($c^2 = 0.160$, $P = 0.205$), whereas the control group subjects were not ($c^2 = 14.24$, $P = 0.001$).

Results

Distribution of the wild-type Val/Val genotype in the study group was 42.7%, of the heterozygote Val/Met genotype 40.9%, and of the polymorphic Met/Met genotype 16.4%, whereas their distributions in the control group were 41.5%, 37.9%, and 20.6%,

respectively. The frequency of the polymorphic Met allele was 36.8% in the study group, whereas it was 39.5% in the control group. When the frequency of the COMT 108/158 Met genotypes (c^2 = 0.985, P = 0.611) or alleles (c^2 = 0.517, P = 0.472) were compared, no significant difference was found between the 2 groups. There was also no significant difference in the genotype and allele frequencies of the COMT Val108/158Met polymorphism between the female control and the female alcoholic groups (c^2 = 0.115, P = 0.735 and c^2 = 0.247, P = 0.884, respectively) or between the male control and the male alcoholic groups (c^2 = 0.485, P = 0.486 and c^2 = 0.728, P = 0.695, respectively). This distribution is summarized in Table 1. According to the genotype frequencies, this study lacks statistical power with 79.1% due to the smallness of study and control groups, giving rise to the conclusion that these results do not confirm the possible association between COMT 108/158 Met variants and alcoholism.

Social backgrounds such as education, occupation, and marital status of the study group among the 3 subgroups of the COMT genotype are summarized in Table 2. No significant differences were observed in any items among these 3 subgroups in the female and male alcoholic subjects. Age at onset of habitual and pathological drinking and admission to alcohol treatment among the 3 subgroups of the COMT genotype are shown in Table 3. According to the results, both male and female alcoholics started to use alcohol habitually at an early age, starting from 15 years of age, and were addicted by the time they were 25-30 years of age; starting therapy was time-consuming for them. Comparisons of variables on alcohol consumption such as drinking amount and frequency among the 3 subgroups of the COMT genotype in the female and male alcoholic subjects are given in Table 4. According to the results, 68.2% (75 of 110) of the subjects drink more than 10 units of alcohol and 96.4% (106 of 110) drink every day. However, in the genotype analyses, no significant differences were observed among these 3 subgroups in any of the study group subjects. Finally, smoking/drug abuse and family history of psychiatric disorders, alcohol dependence, and drug abuse among the 3 subgroups of the COMT genotype in the study group are given in Table 5. The results show that while 88.2% (97 of 110) of the alcoholics are smokers, 8.2% (9 of 110) use both drugs and cigarettes. When the results were evaluated for family history, most of the subjects had no relatives with psychiatric disorders (87.3%, 96 of 110), but for alcoholism, while 36.4% (40 of 110) of the patients had no family history, 63.6% (70 of 110) had either a first- or second-degree alcoholic relative or had observed alcoholism in many family members. However, 91.8% (101 of 110) of the cases had no family history of drug abuse. Moreover, no significant differences were observed in any items among these subgroups in the female and male alcoholic subjects.

Discussion

The results showed that there were no significant differences in the frequency of the Met or Val allele, or the Val/Val, Val/Met, or Met/Met genotypes of the COMT Val108/158Met polymorphism between alcoholics and healthy groups. However, it should be

Table 1. Genotype distributions and allele frequencies of the COMT Val108/158Met polymorphism in the study and control groups.

Groups	Genotype			Allele frequencies		P
	Val/Val	Val/Met	Met/Met	Val	Met	
Study (n = 110)	47 (42.7%)	45 (40.9%)	18 (16.4%)	139 (63.2%)	81 (36.8%)	0.611
Female (n = 10)	3 (30.0%)	5 (50.0%)	2 (20.0%)	11 (55.0%)	9 (45.0%)	0.884
Male (n = 100)	44 (44.0%)	40 (40.0%)	16 (16.0%)	128 (64.0%)	72 (36.0%)	0.695
Control (n = 330)	137 (41.5%)	125 (37.9%)	68 (20.6%)	399 (60.5%)	261 (39.5%)	0.472
Female (n = 101)	40 (39.6%)	39 (38.6%)	22 (21.8%)	119 (58.9%)	83 (41.1%)	0.735
Male (n = 229)	97 (42.4%)	86 (37.6%)	46 (20.0%)	280 (61.1%)	178 (39.9%)	0.486

Table 2. Comparisons of variables of social backgrounds among the 3 subgroups of the COMT genotype in female and male alcoholic subjects (*not available for statistical analyses).

Variables	Female alcoholics (N = 10)			P	Male alcoholics (N = 100)			P
	COMT genotype				COMT genotype			
	Val/Val (N = 3) n (%)	Val/Met (N = 5) n (%)	Met/Met (N = 2) n (%)		Val/Val (N = 44) n (%)	Val/Met (N = 40) n (%)	Met/Met (N = 16) n (%)	
Educational status								
Elementary (n = 42)	1 (33.3%)	2 (66.7%)	0 (0%)	*	19 (48.8%)	13 (33.3%)	7 (17.9%)	0.214
High school (n = 40)	1 (16.7%)	3 (50.0%)	2 (33.3%)	0.521	12 (35.3%)	17 (50.0%)	5 (14.7%)	0.321
University (n = 28)	1 (100.0%)	0 (0%)	0 (0%)	*	13 (48.2%)	10 (37.0%)	4 (14.8%)	0.256
Occupational status								
None (n = 10)	0 (0%)	3 (75.0%)	1 (25.0%)	0.548	3 (50.0%)	3 (50.0%)	0 (0%)	0.526
Official (n = 24)	1 (100.0%)	0 (0%)	0 (0%)	*	13 (56.5%)	9 (39.1%)	1 (4.3%)	0.358
Retired (n = 36)	0 (0%)	1 100.0%)	0 (0%)	*	13 (37.2%)	16 (45.7%)	6 (17.1%)	0.369
Employee (n = 11)	1 (50.0%)	1 (50.0%)	0 (0%)	*	5 (55.6%)	2 (22.2%)	2 (22.2%)	0.412
Others (n = 29)	1 (50.0%)	0 (0%)	1 (50.0%)	*	10 (37.0%)	10 (37.0%)	7 (26.0%)	0.453
Marital status								
Married (n = 75)	2 (40.0%)	1 (20.0%)	2 (40.0%)	0.624	34 (48.6%)	26 (37.1%)	10 14.3%)	0.185
Divorced (n = 20)	0 (0%)	2(100.0%)	0 (0%)	*	7 (38.9%)	7 (38.9%)	4 (22.2%)	0.524
Single (n = 15)	1 (33.3%)	2 (66.7%)	0 (0%)	*	3 (25.0%)	7 (58.3%)	2 (16.7%)	0.412

Table 3. Comparisons of variables of age among the 3 subgroups of the COMT genotype in female and male alcoholic subjects.

Variables of age (years)	**Female alcoholics (N = 10)**						**Male alcoholics (N = 100)**					
	COMT genotype						COMT genotype					
	Val/Val (N = 3)		Val/Met (N = 5)		Met/Met (N = 2)		Val/Val (N = 44)		Val/Met (N = 40)		Met/Met (N = 16)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Onset of habitual drinking	15	3.51	16	3.96	15	2. 12	16	3.17	16	3.89	18	5.51
Onset of pathological drinking	25	4.50	25	9.23	25	0.00	28	8.30	30	10.31	27	10.01
Admission to alcohol treatment	35	4.04	29	9.06	40.0	1.41	40	9.01	43	10.01	36	8.37

Table 4. Comparisons of variables of alcohol consumption among the 3 subgroups of the COMT genotype in female and male alcoholic subjects (*not available for statistical analyses).

Variables	Female alcoholics (N = 10)			P	Male alcoholics (N = 100)			P
	COMT genotype				COMT genotype			
	Val/Val (N = 3) n (%)	Val/Met (N = 5) n (%)	Met/Met (N = 2) n (%)		Val/Val (N = 44) n (%)	Val/Met (N = 40) n (%)	Met/Met (N = 16) n (%)	
Drinking amount								
Drinking ≤10 unit (n = 35)	2 (50.0%)	1 (25.0%)	1 (25.0%)	0.560	20 (64.5%)	7 (22.6%)	4(12.9%)	0.610
Drinking >10 unit (n = 75)	1 (16.7%)	4 (66.7%)	1 (16.7%)	0.582	24 (34.8%)	33 (47.8%)	12 (17.4%)	0.272
Drinking frequency								
1-2 times/month (n = 1)	0 (0%)	0 (0%)	0 (0%)	*	0 (0%)	1 (100.0%)	0 (0%)	*
1-2 times/week (n = 3)	1 (100.0%)	0 (0%)	0 (0%)	*	1 (50.0%)	0 (0%)	1 (50.0%)	*
Every day (n = 106)	2 (22.2%)	5 (55.6%)	2 (22.2%)	0.734	43 (44.3%)	39 (40.2%)	15 (15.5%)	0.421

Table 5. Comparisons of variables of family history of psychiatric disorders, alcohol dependence, and smoking/drug abuse among the 3 subgroups of the COMT genotype in female and male alcoholic subjects (*not available for statistical analyses).

Variables	Female alcoholics (N = 10)			P	Male alcoholics (N = 100)			P
	COMT genotype				COMT genotype			
	Val/Val (N = 3) n (%)	Val/Met (N = 5) n (%)	Met/Met (N = 2) n (%)		Val/Val (N = 44) n (%)	Val/Met (N = 40) n (%)	Met/Met (N = 16) n (%)	
Smoking/drug abuse								
Smokers (n = 97)	3 (30.0%)	5 (50.0%)	2 (20.0%)	0.487	39 (44.9%)	35 (40.3%)	13 (14.8%)	0.246
Drug abusers (n = 4)	0 (0%)	0 (0%)	0 (0%)	*	1 (25.0%)	1 (25.0%)	2 (50.0%)	0.511
Smokers + drug abusers (n = 9)	0 (0%)	0 (0%)	0 (0%)	*	4 (44.4%)	4 (44.4%)	1 (11.2%)	0.489
Relatives with psychiatric disorders								
No cases (n = 96)	3 (37.5%)	3 (37.5%)	2 (25.0%)	0.625	42 (47.7%)	33 (37.5%)	13 (14.8%)	0.312
First-degree (n = 10)	0 (0%)	1 (100.0%)	0 (0%)	*	2 (22.2%)	6 (66.7%)	1 (11.1%)	0.587
Second-degree (n = 4)	0 (0%)	1 (100.0%)	0 (0%)	*	0 (0%)	1 (33.3%)	2 (66.6%)	*
Relatives with alcohol dependence								
No cases (n = 40)	0 (0%)	2 (100.0%)	0 (0%)	*	19 (50.0%)	12 (31.6%)	7 (18.4%)	0.645
First-degree (n = 21)	1 (100.0%)	0 (0%)	0 (0%)	*	7 (35.0%)	7 (35.0%)	6 (30.0%)	0.521
Second-degree (n = 14)	0 (0%)	2 (100.0%)	0 (0%)	*	6 (50.0%)	6 (50.0%)	0 (0%)	0.475
Many family members (n = 35)	2 (40.0%)	1 (20.0%)	2 (40.0%)	0.625	12 (40.0%)	15 (50.0%)	3 (10.0%)	0.254
Relatives with drug abuse								
No cases (n = 101)	3 (37.5%)	5 (62.5%)	0 (0%)	0.654	40 (43.0%)	38 (40.9%)	15 (16.1%)	0.126
First-degree (n = 4)	0 (0%)	0 (0%)	2 (100.0%)	*	2 (100.0%)	0 (33.3%)	0 (0%)	*
Second-degree (n = 5)	0 (0%)	0 (0%)	0 (0%)	*	2 (40.0%)	2 (40.0%)	1 (20.0%)	0.752

pointed out that because the study had less than the desired power (<0.800), a difference was less likely to be detected, so it is not possible to conclude that the presented data did not confirm the significant association in the frequency of COMT Val108/Met polymorphism for the development of alcoholism in Turkish subjects. Therefore, to find a possible association between the Met allele and alcoholism, this study should be evaluated again with an enlarged study group. Moreover, the deviation from the Hardy-Weinberg equilibrium found in the control group is not presently clear.

The results are in contrast with data of previous studies, which do support the hypothesis that the functional COMT Val108/Met polymorphism is linked to alcoholism (5,16-18). Unfortunately, there are actually more studies that either link the high-activity Val allele with alcoholism (19,22,23), or do not support this hypothesis at all, like this study (2,14,15,24,25). This is a common problem with genetic studies of multifactorial diseases, because environmental factors also contribute excessively to their development. This was shown in a study in which the high-activity Val allele was found to be linked with alcoholism and smoking, and the authors claimed that the low-activity Met allele could confer both risk and resilience to alcoholism in different drinking environments (22,26). However, it should also be mentioned that the frequency of the polymorphic *COMT* Met allele in this study was found to be similar to the frequencies of other Turkish groups (27,28). Studies of an Asian population, like in Japan and Korea, had nearly the same number of alcoholic cases as the present study and found similar *COMT* allele frequencies (2,25). Since ethnic differences exist in COMTVal108/158Met polymorphism (29), variations in the frequencies of functionally different COMT alleles are also seen in alcoholism. As a result, it is thought that the genotype distribution and allele frequency of the COMT Val108/158Met gene polymorphism in our study and control groups reflect their real distribution in the Turkish population.

In this study, the ratio of female to male alcoholic subjects was 1:10.. The reason for this discrepancy is that in Turkey, alcohol usage is not very common, and therefore, it is even less common among women. A wide-screen study that evaluated the prevalence of alcohol addiction among males and females in Turkey reported 1.7% for men and 0.1% for women (30). The Turkish population includes many different ethnic groups and a clear subdivision cannot be made. When considering ethnic differences, Turkish alcoholics may resemble more the Asian than the European Caucasian population, since no association between alcoholism and the COMT Val108/Met polymorphism was found in the Asian population (2,24) in contrast to the European Caucasian population (5,16,18).

To further dissect the environmental factors that could contribute to alcoholism, the social backgrounds of the study group were analyzed. Interestingly, most of the subjects had a good social background (i.e. were well educated, employed, and married), and we did not observe any significant differences among the 3 subgroups of the COMT genotype in female and male alcoholic subjects. This was also in good agreement with the results of previous studies (2,16).

The variables related to age among the 3 subgroups of the COMT genotype in the study group were then analyzed. Among the female and male alcoholic subjects, ages at the onset of habitual and pathological drinking were very similar, whereas ages on admission for alcohol treatment were a bit higher in the male alcoholic subjects than the females. Nevertheless, no significant differences were observed, and these results were in good agreement with the results of previous studies (24,31).

In a study in which the low-activity Met allele of the COMT polymorphism was associated with alcohol consumption among social drinkers, the age-adjusted weekly alcohol consumption was higher in the subjects with the low-activity COMT genotype (16). To address this question in the present study group, and to find out if we might see any differences in alcohol consumption among the 3 subgroups of the COMT genotype, we compared the drinking amount and frequencies of the subjects, but found no association between any of these variables and the COMT genotype in the female and male alcoholic subjects.

The high-activity Val genotype and allele were shown to be more prevalent in alcoholic smokers, polysubstance abusers, and individuals meeting

the DSM-III-R substance abuse criteria than in the controls (2,22,23). No significant difference among the different COMT genotypes between the alcoholic and control groups was found in the present study.

Munafo et al. reported that there was an association between the COMT Val108/158Met genotype and cigarette smoking in pregnant women (32), and Nedic et al. found an association between COMT polymorphism and smoking in healthy Caucasian subjects (33). Similar results were found in our violent drunk or sober alcoholics, as the Val/Val genotype and Val allele were slightly more prevalent in these subjects; however, this difference did not reach a level of statistical significance. Ishiguro et al. found that there was an association between either the high- or low-activity polymorphism of the catechol-*O*-methyltransferase gene and alcoholism (2), yet on the other hand, similar to our results, no association was found between the Val allele and alcoholism (24). In a metaanalysis of twin studies, it was shown that the heritability of all addictive substances ranges from 40% to 60%. In the same study, the heritability for alcoholism derived from nearly 10,000 twin pairs was 50% (34). Thus, genetic and environmental factors are almost equally important in alcoholism risk. In a family-based and case-control study of some gene polymorphisms in alcohol dependence, the *COMT* Val108/158Met polymorphism revealed adequate transmissions of alleles to the affected offspring (14). To evaluate whether there is an association between the COMT polymorphism and the family history of psychiatric disorders, alcohol dependence, and drug abuse, the 3 subgroups of the COMT genotype were investigated. An indication of the heritability of alcoholism was also shown, with 64% of the subjects having at least 1 alcoholic relative in their family, but again, no significant association between the heritability of alcoholism and the COMT polymorphism was observed.

In conclusion, the present study does not support the hypothesis that the Met (A) allele of COMT is associated with alcoholism, due to the lack of statistical power; therefore, the study should be repeated in larger groups to find a possible association. Moreover, no association was found between the COMT Val108/158Met polymorphism and some environmental and genetic factors that are known to be involved in the development of alcoholism. However, it would be interesting to further investigate this particular COMT polymorphism together with alcoholism.

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