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ARTICLE

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Association study of a functional catechol-*O*-methyltransferase (COMT) Val$^{108/158}$Met polymorphism and suicide attempts in patients with alcohol dependence

Gordana Nedic[1], Matea Nikolac[1], Korona Nenadic Sviglin[2], Dorotea Muck-Seler[1], Fran Borovecki[3] and Nela Pivac[1]

[1] *Division of Molecular Medicine, Rudjer Boskovic Institute, Zagreb, Croatia*
[2] *Center for Alcoholism and other Addictions, Psychiatric Hospital Vrapce, Zagreb, Croatia*
[3] *Department of Neurology, University Hospital Center Zagreb, Zagreb, Croatia, and Department for Functional Genomics, Center for Translational and Clinical Research, University of Zagreb School of Medicine, University Hospital Center Zagreb, Zagreb, Croatia*

Abstract

Alcohol dependence is frequently associated with aggressive and suicidal behaviour. Genetic factors contribute to both behaviours. Candidate genes, related to suicide and aggression, include genes involved in serotonin, norepinephrine and dopamine pathways. The enzyme catechol-*O*-methyl transferase (COMT) degrades dopamine, epinephrine and norepinephrine. The functional polymorphism (COMT Val$^{108/158}$Met) affects COMT activity, with the valine (Val) variant associated with higher and the methionine (Met) variant with lower COMT activity. This polymorphism is associated with aggressive and suicidal behaviour, but the literature data on this relationship is contradictory and inconsistent. The hypothesis of this study was that Met allele carriers with alcohol dependence will have a higher frequency of suicide attempts compared to other genotypes. Participants were 312 male and 81 female medication-free patients with alcohol dependence and 487 male and 122 female unrelated, non-suicidal medication-free Caucasian healthy subjects. Our results showed significant (χ^2 test with standardized residuals) differences in the frequencies of COMT variants in all alcoholics, alcoholics with different comorbid diagnoses, and in male but not in female alcoholics, with or without suicide attempts. Male alcoholic suicide attempters, compared to male non-attempters, had the higher frequency of Met/Met genotype or Met allele, and significantly (Kruskal–Wallis ANOVA on ranks and Mann–Whitney test) higher aggression and depression scores. These results confirmed the associations between Met allele and aggressive behaviour or violent suicide attempts in various psychiatric diagnoses, and suggested that Met allele of the COMT Val$^{108/158}$ Met might be used as an independent biomarker of suicidal behaviour across different psychopathologies.

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Introduction

Alcohol dependence is frequently associated with suicidal behaviour (Kessler *et al*. 1994) and suicide mortality (Rossow & Amundsen, 1995). Patients with chronic alcoholism have different psychiatric comorbidities, and the most frequent psychiatric disorders related to alcohol use disorders are depression, anxiety, antisocial personality disorder, conduct disorder, and attention deficit hyperactivity disorder (Ducci *et al*. 2007; Sher, 2006). Patients with alcohol dependence have a greater suicide risk than the non-psychiatrically ill subjects, and suicide risk increases if alcoholism is related to comorbid depression (Sher, 2006). Alcoholism is associated with various

Address for correspondence: Dr N. Pivac, Division of Molecular Medicine, Rudjer Boskovic Institute, P. O. Box 180, HR-10002 Zagreb, Croatia.
Tel.: 385 1 4571 207 *Fax*: 385 1 456 1010
Email: npivac@irb.hr

dimensions of personality (novelty seeking, harm avoidance, and reward dependence) and age at onset (Cloninger, 1987). Personality disorders and impulsive and aggressive behaviour, together with a tendency to engage in impulsive violence, are contributory risk factors for suicidal behaviour and completed suicide (Brent *et al*. 1994; Diaconu & Turecki, 2007; Duberstein *et al*. 2000; Dumais *et al*. 2005; McGirr & Turecki, 2007; Sarchiapone *et al*. 2009), both among psychiatric patients as well as in the general population. Twin, family, and adoption studies suggest an important role of genetic factors in suicidal behaviour, with genes playing a role in about 30–50% of cases that involve suicidal behaviour (Bondy *et al*. 2006; Mann *et al*. 1999, 2009; McGuffin *et al*. 2001; Roy *et al*. 1995; Statham *et al*. 1998). Candidate genes thought to be related to suicide are mostly those involved in serotonin and catecholamine pathways [serotonin transporter (SERT or 5-HTT), tryptophan hydroxylase (TPH), monoamine oxidase (MAOA), serotonin receptors (5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A}), catechol-*O*-methyltransferase (COMT), tyrosine hydroxylase (TH) and DOPA decarboxylase] (Mann *et al*. 2009; Slater *et al*. 2009). The association between catecholaminergic dysfunction and suicide behaviour is based on the findings of a higher concentration of norepinephrine and decreased α_2-adrenergic binding in the prefrontal cortex of suicide victims (Arango *et al*. 1993) or lower levels of 3-methoxy-4-hydroxyphenylglycol (a metabolite of norepinephrine) and homovanillic acid (a metabolite of dopamine) in the cerebrospinal fluid of subjects who attempted suicide (Engstrom *et al*. 1999; Jones *et al*. 1990; Roy *et al*. 1986) than in control subjects. Preclinical (Gogos *et al*. 1998; Haller *et al*. 1998), as well as clinical (Tardiff, 1981) data have shown that the elevations in dopamine and norepinephrine levels increase aggressive behaviour. Approximately 30% of violent individuals show a history of self-destructive behaviour, and up to 20% of suicidal subjects have a history of violent behaviour (Mann, 1998). Suicide attempters are more likely to be impulsive and aggressive (Corruble *et al*. 1999; Maiuro *et al*. 1989; Pendse *et al*. 1999; Soloff *et al*. 1994; Weissman *et al*. 1973). It is postulated that increased dopaminergic activity might lead to greater aggression (Gogos *et al*. 1998; Haller *et al*. 1998; Siegel *et al*. 1999), and therefore increased suicidal behaviour.

The enzyme COMT transfers a methyl group to catecholamines like dopamine, epinephrine and norepinephrine, and it is responsible for their degradation (Weinshilboum *et al*. 1999). The enzyme activity is under control of the *COMT* gene. A single base-pair substitution of guanine for adenine results in the replacement of the amino acid valine (Val) with the amino acid methionine (Met) at position 158 ($Val^{158}Met$) in the longer form of the enzyme (membrane-bound COMT or MB-COMT), and at position 108 ($Val^{108}Met$) in the shorter form (soluble COMT or S-COMT). This polymorphism (usually referred as COMT $Val^{108/158}Met$) affects COMT activity (Lachman *et al*. 1996; Lotta *et al*. 1995). The Val variant of COMT has a higher stability and activity, and it catabolizes dopamine up to four times the rate of its Met alternative. A functional $Val^{108/158}Met$ polymorphism in *COMT* gene influences aggressive and anger-related traits in various clinical populations (Kotler *et al*. 1999; Lachman *et al*. 1998; Nolan *et al*. 2000; Strous *et al*. 1997). Since depression and impulsive-aggressive behaviour may contribute to suicidal behaviour, it was suggested that the COMT $Val^{108/158}Met$ polymorphism might represent a risk factor for suicidal behaviour. The literature on the relationship between COMT $Val^{108/158}Met$ and suicidal behaviour is inconsistent, and both an association between the Met allele and completed suicide (Ono *et al*. 2004), suicidal behaviour (Kia-Keating *et al*. 2007) or suicide attempts (Baud *et al*. 2007), or no significant association between suicidal behaviour and COMT $Val^{108/158}Met$ (Russ *et al*. 2000; Zalsman *et al*. 2008) has been reported. The Val/Val genotype was less frequently detected in male suicide completers than in male controls (Ono *et al*. 2004), while that was not the case in female subjects. These results suggest that the COMT $Val^{108/158}Met$ polymorphism affects the catecholaminergic system differently in male and female patients (Ono *et al*. 2004). An explanation for this gender-specific association could be due to the effects of oestrogen in females which modulates neurotransmission and neuronal excitability of the catecholaminergic system (Balthazart *et al*. 1996). Since chronic alcohol abuse increases dopaminergic transmission in the brain, while dopamine mediates the reward processes and alcohol-induced euphoria (Blum *et al*. 2007; Hosák, 2007), subjects with low-activity allele of the COMT might be more vulnerable to develop alcoholism. In line with this, the Met allele, responsible for the low dopamine inactivation, has been reported to be associated with alcoholism (Wang *et al*. 2001), but inconsistencies across studies exist (Hosák, 2007).The Met allele is associated with low COMT activity and this may lead to increased prefrontal dopaminergic activity and increased aggressive behaviour and consequently suicidal behaviour, which may result in suicide attempts. Therefore, the hypothesis of this study was that patients with alcohol dependence who attempted suicide will be more frequently low-activity COMT

carriers (Met allele carriers) than alcoholic patients who did not attempt suicide. Since the association between COMT Val$^{108/158}$Met and suicidal behaviour was detected in male but not in female subjects (Ono *et al*. 2004), the additional aim was to elucidate the association between COMT Val$^{108/158}$Met polymorphism and suicide attempt(s) in ethnically homogenous medication-free male and female patients with chronic alcoholism, who frequently develop suicidal behaviour and attempt suicide (Sher, 2006).

Method

Participants: patients

Participants were 312 male and 81 female ethnically homogenous medication-free patients with alcohol dependence. All subjects were Caucasians of Croatian origin. Alcohol dependence was diagnosed using the Structured Clinical Interview for DSM-IV (SCID; First *et al*. 2000) according to DSM-IV criteria (APA, 1994). Civilian patients with alcohol dependence were admitted into the Psychiatric Hospital Vrapce, due to withdrawal syndrome. Withdrawal symptoms were of the non-psychotic type that intensified 1 wk prior to admission. Most patients were acutely intoxicated with alcohol. Therefore, the interview and the sampling were done when the patients were sober, i.e. at least 12 h after admission to the department. The average age of male and female subjects was 49.39 ± 9.75 and 51.79 ± 11.58 yr, respectively. Based on the SCID and a psychiatric interview, patients with alcohol dependence were subdivided into patients who attempted suicide (suicidal) and patients who did not attempt suicide (non-suicidal), and further into suicidal and non-suicidal patients with or without different comorbid psychiatric diagnoses. There were 59 male patients who attempted suicide and 253 male patients who did not attempt suicide, and 23 female patients with suicide attempts, and 58 female patients without a suicide attempt. Within patients, 163 patients had alcohol dependency without any comorbid diagnoses, while 230 chronic alcoholics had comorbid psychiatric diagnoses: 87 patients had depression, anxiety disorders, or anxious depressive disorders, 130 patients had personality disorders, and 13 patients had developed other comorbidities such as drug abuse, schizophrenia, acute stress reaction, post-traumatic stress disorder, mental retardation, dissociative disorders, organic mental disorders, persistent mood disorders, phobic anxiety disorders, and adjustment disorders. In addition to the SCID and a psychiatric interview, aggression and depressive symptoms were assessed using the Brown–Goodwin Assessment of Life-time Aggression (Brown–Goodwin Scale; Brown *et al.* 1979) and the Hamilton Rating Scale for Depression (HAMD) 17-item scale (Hamilton, 1960). The questionnaire adapted from Brown–Goodwin Scale (Brown *et al*. 1979) consisted of seven behavioural categories (according to Buydens-Branchey *et al*. 1989), translated into Croatian: problems with discipline in the armed forces; problems with discipline at work; assaults on other persons; property damage; incarceration for assaultive behaviour; incarceration for other crimes; crimes that did not result in incarceration. These categories were evaluated with a 0–4 scale (0, lack of any problem; 1, one event; 2, two or a few events; 3, three or several or frequent events; 4, four events or more, or many or numerous events). The total maximum score was 28, and according to Buydens-Branchey *et al*. (1989), a cut-off score of 8 was designated as aggressive behaviour.

Participants: control subjects

The control group consisted of 487 male and 122 female unrelated, medication-free Caucasian healthy subjects of Croatian origin, who were recruited during the period between 2005 and 2009 at the University Hospital Centre Zagreb, Croatia, and who completed the questionnaire answering questions about their medical history, smoking and drinking habits. All individuals gave their detailed medical history. Inclusion criteria were no current medication therapy; no previous or current psychiatric disorders; no drug or alcohol abuse, no suicide attempts; no family history of psychiatric disorders (determined according to the answers of participants about the mental health status of their parents, grandparents, siblings and children); not being related; and belonging to the native ethnic group with at least three generations living in the region.

Written informed consent was obtained from all participants, after explaining the aims and procedures of the study, under guidelines approved by the Ethics Committees of the Psychiatric Hospital Vrapce, and University Hospital Centre Zagreb, Croatia. All human studies have been executed with the full cooperation of participants, adequate understanding, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Blood collection

The sampling of patients with alcoholism was done when the patients were sober, i.e. at least 12 h after admission to the department, at 08:00 hours. Blood

samples (8 ml) from patients and control subjects were drawn in a plastic syringe with 2 ml acid citrate dextrose anticoagulant.

Genotyping

Genomic DNA was extracted from peripheral blood using a salting-out method (Miller *et al*. 1988). The COMT Val$^{108/158}$Met polymorphism was genotyped in an ABI Prism 7000 Sequencing Detection System apparatus (ABI) using a TaqMan-based allele-specific polymerase chain reaction assay, according to the manufacturer's instructions (Applied Biosystems, USA). The primers and probes were purchased from Applied Biosystems as TaqMan® Drug Metabolism Genotyping Assay (assay ID: C_25746809_50; order no.: 43262691).

Statistical evaluation

The results were expressed as means ± standard deviations (S.D.) or numbers and percentages, and evaluated with Sigma Stat 3.5 (Jandell Scientific Corp., USA) and Microsoft Excel. The differences in age were assessed using one-way analysis of variance (ANOVA). The differences in the Brown–Goodwin or HAMD scores were evaluated with Kruskal–Wallis ANOVA on ranks, followed by a non-parametric Mann–Whitney rank sum test, since the normality test failed. Hardy–Weinberg analysis was used to test the equilibrium of the population. The differences in the genotype and allele frequencies were evaluated using a χ^2 test, with Yates correction for continuity, and with standardized residuals (R), to determine what category was a major contributor to rejecting the null hypothesis. The power of calculation (power), which should be 0.800, was evaluated using Sigma Stat 3.5. A Bonferroni correction was used for multiple testing, and the level of significance was set to $\alpha = 0.025$.

Results

To elucidate the possible difference in the frequency of the COMT variants between 312 male and 81 female medication-free Caucasian patients with alcohol dependence (alcoholics), and 487 male and 122 female healthy control non-alcoholic and non-suicidal subjects, the Met/Met, Met/Val and Val/Val genotypes and Met and Val alleles were compared between healthy and alcoholic subjects. The genotype ($\chi^2 = 3.456$, d.f. = 6, $p = 0.738$, power = 0.234) and allele ($\chi^2 = 1.881$, d.f. = 3, $p = 0.587$, power = 0.176) frequency of the COMT Val$^{108/158}$Met did not differ significantly between male and female alcoholic subjects and male and female healthy subjects. These results were confirmed when healthy and alcoholic subjects were not subdivided according to gender, since there was no significant difference in the distribution of the genotypes ($\chi^2 = 1.546$, d.f. = 6, $p = 0.462$, power = 0.174) and alleles ($\chi^2 = 0.997$, d.f. = 1, $p = 0.318$, power = 0.157) between groups. The genotype distribution in male ($\chi^2 = 1.880$, d.f. = 1, $p = 0.170$) or female ($\chi^2 = 0.063$, d.f. = 1, $p = 0.802$) alcoholics, or in male ($\chi^2 = 0.356$, d.f. = 1, $p = 0.551$) or female ($\chi^2 = 0.295$, d.f. = 1, $p = 0.587$) control subjects was in the expected Hardy–Weinberg equilibrium.

Within alcoholic patients, no significant ($\chi^2 = 2.953$, d.f. = 1, $p = 0.086$, power = 0.388) difference was found in the frequency of suicide attempts between male and female alcoholics. Furthermore, the participant groups were matched for age, and there were no significant differences in age of the alcoholics subdivided into male and female alcoholics with or without suicide attempts (Table 1). Since the power of calculation was below the desired power of 0.800, these results should be repeated on larger samples.

There were no significant differences from the expected Hardy–Weinberg equilibrium in the genotype distribution in male alcoholics with suicide attempts ($\chi^2 = 0.068$, d.f. = 1, $p = 0.794$) or male alcoholics without suicide attempts ($\chi^2 = 3.471$, d.f. = 1, $p = 0.062$), or in female alcoholics with suicide attempts ($\chi^2 = 0.016$, d.f. = 1, $p = 0.899$) or female alcoholics without suicide attempts ($\chi^2 = 0.172$, d.f. = 1, $p = 0.678$).

Table 1 shows the significant differences (after Bonferroni correction) in the frequencies of Met/Met, Met/Val and Val/Val genotypes, Met and Val alleles, and Val carriers *vs.* homozygous Met/Met genotype, between male alcoholics with or without suicide attempts. These differences were due to the significantly higher frequency of Met/Met genotype (44.1%) in male alcoholics who attempted suicide compared to male alcoholics who did not attempt suicide (19.8%). The absolute values of the standardized residuals for the Met/Met genotype compared to other COMT genotypes, and for the homozygous Met/Met genotype compared to Val carriers were $R = 3.07$ and $R = 3.20$, respectively, confirming their major contribution to the significant effect in the χ^2 statistics. These data had enough statistical power ($p > 0.800$) to detect significant effect. Within female alcoholics with or without suicide attempts, no significant difference in the frequency of COMT variants was found, but the lack of significant differences might be due to the lack of power (Table 1).

To evaluate the possible influence of gender on the COMT variants and suicide attempt (Ono *et al*. 2004),

Table 1. COMT Val$^{108/158}$Met variants in male and female alcoholics with suicide attempt (suicidal) or without suicide attempt (non-suicidal)

	Alcoholics ($N=393$)			
	Men ($n=312$)		Women ($n=81$)	
	Suicidal ($n=59$) No. (%)	Non-suicidal ($n=253$) No. (%)	Suicidal ($n=23$) No. (%)	Non-suicidal ($n=58$) No. (%)
Genotypes				
Met/Met	26 (44.1)	50 (19.8)	9 (39.1)	15 (25.9)
Met/Val	27 (45.7)	141 (55.7)	11 (47.8)	29 (50.0)
Val/Val	6 (10.2)	62 (24.5)	3 (13.1)	14 (24.1)
χ^2 test	$\chi^2=16.997$, d.f. $=2$, $p<0.001$, power $=0.977$		$\chi^2=1.960$, d.f. $=2$, $p=0.375$, power $=0.211$, n.s.	
Alleles				
Met	79 (67.0)	241 (47.6)	29 (63.0)	59 (50.9)
Val	39 (33.0)	265 (52.4)	17 (37.0)	57 (49.1)
χ^2 test, Yates correction	$\chi^2=13.534$, d.f. $=1$, $p<0.001$, power $=0.972$		$\chi^2=1.509$, d.f. $=1$, $p=0.219$, power $=0.217$, n.s.	
Val carriers				
Val/Val + Met/Val	33 (55.9)	203 (80.2)	14 (60.9)	43 (74.1)
Met/Met	26 (44.1)	50 (19.8)	9 (39.1)	15 (25.7)
χ^2 test, Yates correction	$\chi^2=14.048$, d.f. $=1$, $p<0.001$, power $=0.977$		$\chi^2=0.827$, d.f. $=1$, $p=0.363$, power $=0.138$, n.s.	
	Mean $\pm$ S.D.	Mean $\pm$ S.D.	Mean $\pm$ S.D.	Mean $\pm$ S.D.
Age (yr)	50.58 ± 9.17	49.12 ± 9.88	50.35 ± 10.01	52.36 ± 12.18
ANOVA	$F=1.738$, d.f. $=3, 389$, $p=0.159$, power $=0.201$, n.s.			

n.s., Not significant.
Frequencies (in %) are shown in parentheses.

Met/Met, Met/Val and Val/Val genotypes and Met and Val alleles were compared in male and female alcoholics with and without suicide attempts. No significant gender-related differences were found in the frequencies of the genotypes ($\chi^2=0.234$, d.f. $=2$, $p=0.889$) or alleles ($\chi^2=0.084$, d.f. $=1$, $p=0.771$) in alcoholic men and women with suicide attempts, or in the genotypes ($\chi^2=0.185$, d.f. $=2$, $p=0.912$) or alleles ($\chi^2=0.006$, d.f. $=1$, $p=0.916$) in male and female alcoholics who did not attempt suicide. However, power of calculation (0.056–0.066) was below the desired power of 0.800, indicating that we might have failed to detect gender-related differences in COMT variants between male and female alcoholics with and without suicide attempts. When the data from male and female alcoholics were collapsed, significant differences were detected in the frequencies of the genotypes ($\chi^2=18.484$, d.f. $=2$, $p=0.001$, power $=0.987$) or alleles ($\chi^2=16.020$, d.f. $=1$, $p=0.001$, power $=0.989$) between alcoholics with or without suicide attempts. These data confirmed the results obtained in male alcoholics, and showed with a high statistical power that the higher frequency of the Met/Met genotype ($R=3.13$) in suicidal alcoholics contributed to the significance of the χ^2 statistics.

Since COMT Val$^{108/158}$Met variants might be associated with smoking, as was shown for healthy subjects (Nedic *et al*. 2010), we additionally evaluated the effect of smoking in male or female alcoholics with or without suicide attempts. The frequency of genotypes did not differ significantly between male alcoholic smokers and non-smokers with ($\chi^2=0.798$, d.f. $=2$, $p=0.671$, power $=0.110$) or without ($\chi^2=0.672$, d.f. $=2$, $p=0.714$, power $=0.100$) suicide attempts, or between female alcoholic smokers and non-smokers with ($\chi^2=1.312$, d.f. $=2$, $p=0.519$, power $=0.154$) or without ($\chi^2=2.340$, d.f. $=2$, $p=0.310$, power $=0.246$) suicide attempts.

As suicide attempts in alcoholism are usually associated with increased aggression, and/or comorbid depression (Buydens-Branchey *et al*. 1989; Sher, 2006), in the subsequent analyses we evaluated genotype-related differences in the mean total scores in the modified Brown–Goodwin Scale and HAMD scores between alcoholics with or without suicide attempts. In male, but not in female alcoholics with or without

Table 2. Comparisons of the total aggression scores, evaluated using the modified Brown–Goodwin Scale, among the COMT Val$^{108/158}$Met genotype groups in male and female alcoholics

	Total scores on the modified Brown–Goodwin Scale (COMT Val$^{108/158}$Met)			
	AA (Met/Met)	AG (Met/Val)	GG (Val/Val)	Kruskal–Wallis ANOVA on ranks
Male alcoholics				
With suicide attempt	7.58 ± 5.55	7.07 ± 4.16	8.33 ± 4.72	$H = 15.060$, d.f. = 5, $p = 0.010$, power = 0.738
Without suicide attempt	4.50 ± 3.94*	4.96 ± 4.48**	5.76 ± 4.30	
Female alcoholics				
With suicide attempt	3.44 ± 1.94	2.82 ± 3.28	7.00 ± 3.61	$H = 7.909$, d.f. = 5, $p = 0.161$, power = 0.161, n.s.
Without suicide attempt	2.07 ± 2.02	2.34 ± 3.20	3.57 ± 4.85	

n.s., Not significant.
* $p = 0.019$ *vs.* the scores in male alcoholics with Met/Met genotype with suicide attempt; ** $p = 0.017$ *vs.* the scores in male alcoholics with Met/Val genotype with suicide attempt (Mann–Whitney test).

Table 3. Comparisons of the total HAMD scores among the COMT Val$^{108/158}$Met genotype groups in male and female alcoholics

	Total HAMD scores (COMT Val$^{108/158}$Met)			
	AA (Met/Met)	AG (Met/Val)	GG (Val/Val)	Kruskal–Wallis ANOVA on ranks
Male alcoholics				
With suicide attempt	23.23 ± 8.32	23.89 ± 6.64	19.33 ± 4.88	$H = 17.659$, d.f. = 5, $p = 0.003$, power = 0.840
Without suicide attempt	17.94 ± 6.52*	19.58 ± 7.13**	21.29 ± 7.70	
Female alcoholics				
With suicide attempt	22.78 ± 5.40	24.91 ± 5.12	28.33 ± 2.52	$H = 6.144$, d.f. = 5, $p = 0.292$, power = 0.050, n.s.
Without suicide attempt	22.87 ± 12.66	21.31 ± 7.50	21.57 ± 8.86	

HAMD, Hamilton Rating Scale for Depression; n.s., not significant.
* $p = 0.008$ *vs.* the scores in male alcoholics with Met/Met genotype with suicide attempt; ** $p = 0.005$ *vs.* the scores in male alcoholics with Met/Val genotype with suicide attempt (Mann–Whitney test).

suicide attempts, Kruskal–Wallis ANOVA on ranks revealed significant genotype-related differences in the Brown–Goodwin (Table 2) and HAMD (Table 3) scores.

Significantly higher (Mann–Whitney test) aggression scores (evaluated using the modified Brown–Goodwin Scale) were detected in male alcoholics with suicide attempts, who were carriers of Met/Met ($p = 0.019$) or Met/Val ($p = 0.017$) genotypes than in the corresponding male alcoholics without suicide attempts who were carriers of Met/Met or Met/Val genotypes. The aggression scores did not differ significantly between female alcoholics subdivided according to the COMT variants, with or without suicide attempts. Although male alcoholics had higher aggression scores than female alcoholics, significant gender-related differences were found only between male alcoholic patients with the Met/Val genotype with ($p = 0.013$) or without ($p = 0.001$) suicide attempts compared to the scores in the corresponding female alcoholic patients with the Met/Val genotype with or without suicide attempts (Table 2).

The total scores in the HAMD, showing the severity of depressive symptoms, were significantly (Mann–Whitney test) higher in male alcoholics with suicide attempts, who were carriers of Met/Met ($p = 0.008$) or Met/Val ($p = 0.005$) genotypes than in the corresponding male alcoholics without suicide attempts who were carriers of Met/Met or Met/Val genotypes. There was no significant difference in the HAMD scores between female alcoholics with different COMT variants with or without suicide attempts. Female alcoholics who attempted suicide with the Val/Val genotype had significantly ($p = 0.024$) higher HAMD scores than male alcoholics who attempted suicide with the Val/Val genotype (Table 3).

Table 4. COMT Val$^{108/158}$Met variants in male and female suicidal and non-suicidal alcoholics, subdivided further into alcoholics without and with comorbid diagnoses

	Alcoholics without comorbid diagnoses ($N=163$)			
	Men ($n=137$)		Women ($n=26$)	
	Suicidal ($n=8$) No. (%)	Non-suicidal ($n=129$) No. (%)	Suicidal ($n=5$) No. (%)	Non-suicidal ($n=21$) No. (%)
Genotypes				
Met/Met	2 (25.0)	29 (22.5)	3 (60.0)	7 (33.3)
Met/Val	5 (62.5)	73 (56.6)	2 (40.0)	9 (42.9)
Val/Val	1 (12.5)	27 (20.9)	0 (0.0)	5 (23.8)
χ^2 test	$\chi^2=0.329$, d.f. $=2$, $p=0.484$, power $=0.073$, n.s.		$\chi^2=1.945$, d.f. $=2$, $p=0.378$, power $=0.210$, n.s.	
Alleles				
Met	9 (56.3)	131 (50.8)	8 (80.0)	23 (54.8)
Val	7 (43.7)	127 (49.2)	2 (20.0)	19 (45.2)
χ^2 test, Yates correction	$\chi^2=0.028$, d.f. $=1$, $p=0.867$, power $=0.050$, n.s.		$\chi^2=1.217$, d.f. $=1$, $p=0.270$, power $=0.183$, n.s.	
	Alcoholics with comorbid diagnoses ($N=230$)			
	Men ($n=175$)		Women ($n=55$)	
	Suicidal ($n=5$) No. (%)	Non-suicidal ($n=124$) No. (%)	Suicidal ($n=18$) No. (%)	Non-suicidal ($n=37$) No. (%)
Genotypes				
Met/Met	24 (47.1)	21 (16.9)	6 (33.3)	8 (21.6)
Met/Val	22 (43.1)	68 (54.9)	9 (50.0)	20 (54.1)
Val/Val	5 (9.8)	35 (28.2)	3 (16.7)	9 (24.3)
χ^2 test	$\chi^2=19.080$, d.f. $=2$, $p=0.001$, power $=0.988$		$\chi^2=1.016$, d.f. $=2$, $p=0.602$, power $=0.050$, n.s.	
Alleles				
Met	70 (68.6)	100 (42.0)	21 (58.3)	36 (48.7)
Val	32 (31.4)	138 (58.0)	15 (41.7)	38 (51.3)
χ^2 test, Yates correction	$\chi^2=19.174$, d.f. $=1$, $p=0.001$, power $=0.997$		$\chi^2=0.563$, d.f. $=1$, $p=0.453$, power $=0.108$, n.s.	

n.s., Not significant.
Frequencies (in %) are shown in parentheses.

In order to explore the possible influence of comorbid diagnoses on COMT variants in alcoholic patients with and without suicide attempts, male and female suicide attempters and non-attempters were subdivided into groups without and with comorbid psychiatric diagnoses (mostly depression, anxiety and personality disorders). As shown in Table 4, significant differences were found in the frequencies of Met/Met, Met/Val and Val/Val genotypes, and Met and Val alleles between male, but not female, suicidal and non-suicidal alcoholics, with comorbid psychiatric diagnoses. This significance was induced by a higher frequency of the Met/Met genotype (47.1%) in male suicidal alcoholics compared to male non-suicidal alcoholics (16.9%), showing a significant contribution of the Met/Met genotype ($R=3.01$). The frequencies of Met/Met, Met/Val and Val/Val genotypes, and Met and Val alleles did not differ significantly within suicidal and non-suicidal male or female alcoholics without comorbid psychiatric diagnoses (Table 4). Due to the smaller numbers, these data lacked the statistical power ($p<0.800$).

Discussion

This study provides the first evidence of the significant association between the COMT Val$^{108/158}$Met polymorphism and suicide attempts in ethnically homogenous Caucasian groups of medication-free patients with alcohol dependence. Our results showed significant differences in the frequencies of COMT variants (i.e. Met/Met, Met/Val and Val/Val genotypes, Met or Val alleles, or Val carriers *vs.* homozygous Met/Met genotype) among male, but not female alcoholics with or without suicide attempts. Namely, alcoholic men who attempted suicide had the higher frequency of the Met/Met genotype or the Met allele than alcoholic men who did not attempt suicide. When the data from male and female alcoholic patients were collapsed, suicide attempts were significantly associated with the Met/Met genotype and the Met allele, confirming an involvement of the Met/Met genotype in the development of suicidal behaviour in alcoholic patients. In agreement with our results, the Val/Val genotype was less frequently detected in male suicide completers than in male controls (Ono *et al*. 2004), suggesting that Val/Val could be a factor that protects against suicide, especially in male patients, and that the Met allele, independently of diagnosis, may be a risk factor for violent suicide. Our data are in line with a meta-analysis showing a significant association between the COMT Val$^{108/158}$Met polymorphism and suicidal behaviour (Kia-Keating *et al*. 2007), and with evidence for an association of the COMT polymorphism and suicide attempts in schizophrenia and schizoaffective patients (Kotler *et al*. 1999; Lachman *et al*. 1998; Nolan *et al*. 2000; Strous *et al*. 1997). An association between the Met/Met genotype and violent suicide attempts was also found in other studies (Nolan *et al*. 2000; Rujescu *et al*. 2003), which indicates that the Val$^{108/158}$Met polymorphism may modify the clinical phenotype of suicidal behaviour. The Met allele is associated with low COMT activity and this may lead to increased prefrontal dopaminergic activity and increased aggressive behaviour. Our results have confirmed the hypothesis that the low COMT activity variant is associated with suicide attempts. This significant association was not influenced by smoking, which is related to higher frequency of the Val/Val genotypes in smokers (Nedic *et al*. 2010; Tochigi *et al*. 2007), as our data showed that tobacco smoking did not significantly affect the frequency of COMT variants in male or female alcoholic smokers and non-smokers with or without suicide attempts. In our study, the control group was used to compare the frequencies in COMT variants between chronic alcoholics and control subjects in an ethnically homogenous group of Caucasians of Croatian origin. Although we expected that the Met/Met genotype would be associated with alcoholism due to the lower COMT activity and more dopamine release in the brain, and the consequently elevated rewarding effects of alcohol consumption (Blum *et al*. 2007), our results showed a similar distribution of the COMT variants between male and female alcoholics and healthy control male and female subjects, or between all alcoholics and all control subjects. This finding disagrees with previously published data (Tiihonen *et al*. 1999), presumably due to differences in sample sizes and differences in the inclusion of only late-onset alcoholics *vs.* both early and late-onset alcoholics in the present study. Therefore, COMT Val$^{108/158}$Met was associated with suicide attempts in alcoholism, but not with alcoholism as a diagnostic entity, or with smoking.

In contrast to our data, some reports have found no differences in the genotype frequencies of functional polymorphisms in the *COMT* gene between suicidal in-patients and control subjects (De Luca *et al*. 2005; Liou *et al*. 2001; Russ *et al*. 2000; Zalsman *et al*. 2008), and one study even found that the Val/Val genotype was more frequently detected in suicide attempters than in normal controls (Baud *et al*. 2007). These differences between studies might be explained by the different diagnostic entities used across the studies, since we evaluated patients with alcohol dependence, while other studies included patients with schizophrenia, schizoaffective or mood disorders. Furthermore, we compared alcoholics who attempted and who never attempted suicide, while other studies evaluated patients with suicidal behaviour (which includes suicide ideation, thoughts and plans in addition to attempts).

Similarly to the lack of significant differences reported between female suicide completers and controls in either genotype or allele frequencies (Ono *et al*. 2004), we did not detect significant differences in the COMT variants between female alcoholics with or without suicide attempts. This lack of significant association was due to the smaller number of female alcoholics in the present study, and a lack of statistical power, since female alcoholic patients who attempted suicide also had a marginally higher frequency of the Met/Met genotype (39.1%) than female alcoholics who did not attempt suicide (25.9%), and in addition, suicidal alcoholic women had a slightly lower frequency of the Val/Val genotype (13.1%) than female alcoholics without suicide attempts (24.1%). Namely, the data found in female alcoholics with or without suicide attempts were similar to genotype and allele

frequencies detected in the larger groups of corresponding male alcoholics, and when the data from both genders were collapsed, and had enough statistical power, all alcoholics with suicide attempts had significantly higher frequency of the Met/Met genotypes than those without suicide attempts.

In contrast to data showing that a higher proportion of females attempt suicide in the USA (Kia-Keating *et al*. 2007), although men are more successful in committing suicide, in our study there was a similar frequency of suicide attempts between male and female alcoholics of Croatian origin.

Gender-related differences were not detected in the frequency of COMT variants between alcoholic patients with or without suicide attempts, due to the much smaller number of female alcoholics, consequent lack of power of calculation, and the type I error, which represents a limitation of the study. On the other hand, clear gender-related differences were found in the scores measuring aggression and depression. All aggression scores were higher in male than in female alcoholic patients, while male alcoholics with the Met/Val genotype, with or without suicide attempts, had significantly higher aggression scores than the corresponding female alcoholics. Within male alcoholics, those with suicide attempts, or carriers of Met/Met or Met/Val genotypes, had significantly higher Brown–Goodwin Scale scores and HAMD scores, than those without suicide attempts who were carriers of the corresponding genotypes. The finding of the higher aggression scores in our alcoholic suicidal Met carriers agrees with the significant association detected between the Met allele and a history of violent suicide attempts in male, but not in female schizophrenic and schizoaffective patients (Nolan *et al*. 2000), or between the Met/Met genotype and aggression in male homicidal schizophrenia patients (Kotler *et al*. 1999), or between the Met allele and violent suicide attempts in patients with various psychiatric diagnoses (Rujescu *et al*. 2003), suggesting a major role of catecholaminergic pathways in the mediation of self- and other-directed aggression (Nolan *et al*. 2000). Our results are not in line with the lack of significant association between COMT variants and violence or suicide attempts in schizophrenia patients (Liou *et al*. 2001), or between COMT variants and a history of suicide attempts, and lethality or method of suicide attempt, or with aggressive/impulsive traits in the large group of mood disorder subjects (Zalsman *et al*. 2008).

The low COMT activity variant might present a risk factor for violent suicide, independent of diagnosis (Rujescu *et al*. 2003), since the Met/Met genotype was associated with higher scores on anger-related traits (Rujescu *et al*. 2003). This is in line with the higher frequency of the Met/Met genotype in suicidal compared to non-suicidal male alcoholics with different comorbid psychiatric diagnoses. Although alcoholic patients without comorbid diagnoses had similar frequency of the COMT variants, this result might be due to a lack of the statistical power, and the fact that chronic alcoholic patients frequently develop other comorbid diagnoses (Ducci *et al*. 2007; Sher, 2006). In agreement with the proposed risk factors for attempted and completed suicide in alcoholism, such as high aggression and impulsivity, alcoholism severity, major depressive episode, stressful life events, social problems and hopelessness (Sher, 2006), our results suggest that Met carriers with chronic alcoholism and comorbid depression, anxiety and personality disorders are at risk of attempting suicide. Our data might be explained by the fact that carriers of the low COMT activity variants are more prone to develop aggression due to poor dopamine metabolism, and therefore have increased concentrations of prefrontal dopamine which may be associated with aggressive behaviour and increased expression of anger-related traits (Rujescu *et al*. 2003), and suicide behaviour.

Within female alcoholic patients, there were no significant differences in the aggression and depression scores between carriers of COMT variants with or without suicide attempts. These results disagree with the gender-mediated effect on two State-Trait Anger Expression Inventory subscales – Trait Anger and Anger Control, since it has been reported that the Val/Val genotype markedly affects the scores in female suicide attempters (Baud *et al*. 2007), while in our study this association was marginal but not significant. The HAMD scores were significantly higher in female suicidal alcoholics with the Val/Val genotype compared to the corresponding male suicidal alcoholics, showing that alcoholic women frequently develop depressive symptoms. These results indicate that the COMT genotype might have a possible gender-related effect on a personality trait (Baud *et al*. 2007).

In conclusion, we have found that Met carriers were over-represented in male alcoholic suicide attempters, in all alcoholics, and in alcoholics with comorbid psychiatric diagnoses. In addition, male alcoholic suicide attempters who were Met carriers showed higher levels of aggression and depression than the corresponding non-attempters, confirming the associations previously found between the Met allele with aggressive behaviours or violent suicide attempts in schizophrenia (Kotler *et al*. 1999; Lachman *et al*. 1998;

Nolan *et al*. 2000; Strous *et al*. 1997) or depressive disorders (Ohara *et al*. 1998). Our results confirmed that the Met allele of the COMT Val$^{108/158}$Met polymorphism might be used as an independent biomarker of suicidal behaviour across different psychopathologies.

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Statement of Interest

None.

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