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COMT and *BDNF* gene variants help to predict alcohol consumption in alcohol-dependent patients

Klimkiewicz Anna, MD, PhD[1], **Mach Anna, PhD**[1], **Jakubczyk Andrzej, MD, PhD**[1], **Klimkiewicz Jakub, MD, PhD**[2], **Wnorowska Anna, MD, PhD**[1], **Kopera Maciej, MD, PhD**[1], **Fudalej Sylwia, MD, PhD**[1], **Burmeister Margit, PhD**[3], **Brower Kirk, MD, PhD**[3], and **Wojnar Marcin, MD, PhD**[1,3]

[1]Department of Psychiatry, Medical University of Warsaw, 27 Nowowiejska St., 00-665 Warsaw, Poland [2] Department of Anesthesiology and Intensive Therapy, Military Institute of Medicine, 128 Szaserów St., 04-141 Warsaw, Poland [3]Department of Psychiatry, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5295, MI, USA

Abstract

Background—The neurobiology of alcohol dependence (AD) involves alterations in neurotransmitters and the stress response. We hypothesized that an interaction between functional variants of dopaminergic and neurotrophic genes may influence drinking in AD.

Methods—The relationship between alcohol consumption and single nucleotide polymorphisms (SNPs), Val66Met in the *BDNF* and Val158Met in the *COMT,* was analyzed among 281 alcohol-dependent individuals.

Results—Individuals carrying both the *COMT* Met158Met genotype and the *BDNF* Val66Val genotype drank more than those with other variants of these genes (p=0.039). Those who had a family history of AD also drank more than those without a family history (p = 0.048). Patients with both Met/Met genotype in the *COMT* Val158Met polymorphism and Val/Val genotype in the *BDNF* Val66Met polymorphism suffered from more health problems than those carrying other variants (p=0.030) and had lower motivation to change drinking patterns (p = 0.031).

Conclusions—Patients carrying both the *BDNF* Val66Val and *COMT* Met158Met variants had higher alcohol consumption. These effects may be influenced by the effects of *BDNF* and *COMT* on dopamine responses to alcohol. Motivation-enhancing strategies might benefit the group of patients identified by genotyping in this study as well as treatment aimed at reducing alcohol consumption.

Keywords

alcohol dependence; gene polymorphism; treatment; reduction of alcohol consumption

Corresponding author: Sylwia Fudalej, M.D., Ph.D., Department of Psychiatry, Medical University of Warsaw, 27 Nowowiejska St., 00-665 Warsaw, Poland, Phone: +48 22 825 1236, Fax: +48 22 825 1315, sylwia@wum.edu.pl.

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1.1 Introduction

Alcohol dependence is a multifactorial disease, in which genetic factors play an important role. Previous genetic studies on alcoholism suggested the existence of functional variants of selected genes that influence drinking behavior and are risk factors for alcohol dependence (Hallikainen et al., 1999, Wojnar et al., 2009, Wang et al., 2011, Bach et al., 2015, Plemenitas et al., 2015). It is known that the neurobiology of alcoholism involves alterations in neurotransmitter systems, e.g., the dopaminergic system (Gilpin and Koob, 2008, Karkhanis et al., 2015, Vasconcelos et al., 2015). Both the catechol-O-methyltransferase (*COMT*) and the brain-derived neurotrophic factor (*BDNF*) genes are well investigated. They play a crucial role in the functioning of the central dopaminergic system, which is implicated in various neuropsychiatric disorders.

COMT is a post-synaptic enzyme, which is involved in degradation of catecholamines: dopamine, norepinephrine and epinephrine (Pavlov et al., 2012). As many as 345 polymorphisms have been identified in the *COMT* gene mapped to chromosome 22q11.1–q11.2 with a size of about 27 Kbp. One functional single nucleotide polymorphism (SNP) (rs4680) is due to a guanine-to-adenine transition at codon 158 resulting in valine (Val) to methionine (Met) substitution. It is thought that this polymorphism influences dopamine concentration primarily in the prefrontal cortex (Akil et al., 2003). Carriers of the Val158 allele synthesize a form of the enzyme with enhanced thermostability (Lachman et al., 1996), which displays a 40% higher brain activity than the Met158 allele at normal body temperature. Since the two alleles behave additively, the heterozygotes will display an intermediate activity (Weinshilboum et al., 1999). The low-activity Met158 allele is reported to be related to higher extracellular dopamine levels in prefrontal cortical areas, being associated with better performance on executive cognition tasks (Dumontheil et al., 2011), while the Val158 allele has been associated with advantageous processing of aversive stimuli (Mier et al., 2010). This polymorphism has been identified as a risk factor for various neuropsychiatric disorders, including substance use and dependence, obsessive-compulsive disorder, and attention deficit hyperactivity disorder (ADHD) (Hosak, 2007). Several studies reported an association between the low-activity *COMT* allele or genotype and alcohol problems (Kauhanen et al., 2000, Wang et al., 2001, Guillot et al., 2015).

It was also shown that the high-activity *COMT* allele (Val158) is more prevalent in those who use more than one psychoactive substance (polysubstance users) (Vandenbergh et al., 1997) and heroin addicts (Horowitz et al., 2000).

BDNF is a neurotrophin that plays an important role in the growth, differentiation, and survival of neurons. BDNF is known to support the activity of dopaminergic, glutaminergic, cholinergic, and serotonergic neurons. BDNF is involved in the stimulation of forebrain dopamine release and prevention of damage of dopaminergic neurons (Lee et al., 2013). In mutant mice in the midbrain–hindbrain regions, where the *BDNF* gene was selectively deleted, the number of tyrosine hydroxylase-expressing dopaminergic neurons was found to be reduced (Baquet et al., 2005).

The *BDNF* gene is encoded on the human chromosome 11p13. The most investigated SNP in the *BDNF* gene is Val66Met (rs6265). This SNP is linked to guanine substitution of adenine in a highly unstable region, at position 196 of the gene sequence coding for the precursor of BDNF (proBDNF). Amino acid substitution leads to a substitution from valine (Val) to methionine (Met) at codon 66, which has functional consequences. This SNP has been associated with decreased activity-dependent BDNF secretion from cultured hippocampal neurons (Egan et al., 2003). The Met allele has been associated with impairments in intracellular trafficking and activity-dependent secretion of BDNF in neurons (Chen et al., 2006).

In alcohol dependence, this functional *BDNF* SNP has been previously associated with greater severity and earlier onset of illness and early relapse (Matsushita et al., 2004, Wojnar et al., 2009, Grzywacz et al., 2010). Studies have shown that the Met66 allele has also been associated with violent behavior and a history of delirium tremens in alcohol-dependent patients (Matsushita et al., 2004). Some other studies have shown that the association between the *BDNF* Val66Met polymorphism and alcoholism are conflicting and inconsistent (Wojnar et al., 2009, Grzywacz et al., 2010, Shin et al., 2010, Nedic et al., 2013). It is notable that ethnic and population differences exist in the frequency of the *BDNF* Val66Met genotypes. In the European population, the Val66 allele is present in 80%, whereas in the Asian population only in 50% (Pivac et al., 2009).

Because dopamine release is an important effect during alcohol intoxication, the aim of our study was to examine the relationship between dopamine-sensitive *COMT* and *BDNF* polymorphisms, and their association with drinking behavior in alcohol-dependent individuals. Based on previous studies, we hypothesized that the interaction between functional dopaminergic and neurotrophic genes variants may influence drinking behavior of patients with alcohol dependence. To the best of our knowledge, there is no other research examining the combination of these genes in relationship to clinical aspects of alcohol dependence.

1.2 Material and methods

Participants were 281 patients consecutively admitted to four alcohol treatment programs in Warsaw, Poland. All programs were abstinence-based, combining group and individual therapy, and included elements of 12-step facilitation therapy and relapse prevention. There were 212 male and 69 female participants, with an average age of 43.1 years (SD = 0.6). All participants were European Caucasians.

This was a cross-sectional, naturalistic study of the relationship between genetic variants of *BDNF* and *COMT*, and alcohol consumption. Only patients with a diagnosis of alcohol dependence were eligible to participate. Diagnoses were made according to DSM-IV criteria, based on clinical interview and confirmation with the M.I.N.I. International Neuropsychiatric Interview (Sheehan et al., 1998). Exclusion criteria were age under 18, a psychotic disorder, acute alcohol withdrawal, current pharmacotherapy for comorbid psychiatric disorders, cognitive impairment, and presence of aggressive or self-harm behavior. All participants gave written informed consent. The protocol was approved by the

Bioethics Committee at the Medical University of Warsaw and the University of Michigan Institutional Review Board.

1.2.1 Measures

Demographic data were obtained using a modified version of the University of Arkansas Substance Abuse Outcomes Module (SAOM) (Smith et al., 2006), a self-administered questionnaire. Alcohol consumption per drinking day was calculated from the *Time-Line Follow-Back Interview* (TLFB) (Sobell et al., 1979). One standard drink of alcohol was defined as the amount of an alcoholic beverage containing 10g of ethanol. The general health subscale from the SF-36 health survey questionnaire (SF36) (Hunt and McKenna, 1992), a self-administered inventory, was used to evaluate general health status. Scores were converted to standardized T-scores with higher scores indicating better health. Motivation to change drinking patterns was measured with the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) (Isenhart, 1997) with higher scores indicating greater motivation. A history of alcohol dependence among family members was established based on a single question (yes/no). Economic status was recognized by asking patients about having enough money to cover their everyday needs (yes/no).

DNA was derived from white blood cells collected from the participants by the research team. We extracted DNA using the Gentra Pure Gene blood kit accordingly to the instructions (Qiagen). We analyzed the SNPs, Val66Met (rs6265) in the *BDNF* gene (11p13) and Val158Met (rs4680) in the *COMT* gene (22q11), using the LightSNiP typing assay (TIB-MolBiol, Berlin, Germany) with the LightCycler 480 instrument/system (Roche Diagnostics). The samples were genotyped at the University of Michigan with inventoried Taqman assays (Applied Biosystems ABI, Foster City, CA), and run on the University of Michigan DNA Core facility's ABI PRIZM 7900HT sequence analyzer. Genotype concordance was 98%.

Statistical analysis was performed using Statistica software. The data distribution was examined using the Kolmogorov-Smirnov test. Due to non-normal distributions of variables, we used the Mann-Whitney test in further analyses. All variables that were significant in the bivariate analyses as well as control demographic variables (age, gender, employment, living situation [alone or not], and economic status) were simultaneously entered in the linear regression analysis in order to compare the significance of the correlates of alcohol consumption. P-value < 0.05 was considered as statistically significant.

1.3 Results

In the study population of 281 alcohol-dependent individuals entering addiction treatment programs, the mean daily consumption on drinking days was 195.8 g (SD: 135.0) of ethanol, with a median of 169.0 g (quartiles: 126.5; 135.0). Mean daily alcohol consumption among men was 208.3 g (SD: 147.6), among women – 154.7 g (SD: 74.0).

Both *COMT* Val158Met and *BDNF* Val66Met polymorphisms were consistent with Hardy-Weinberg equilibrium. Genotype and allele distribution is presented in Table 1.

We found that co-occurrence of *COMT* Met158Met genotype and *BDNF* Val66Val genotype (N=51) was associated with higher alcohol consumption. Individuals carrying these genotypes jointly drank more (median: 19.3 drinks per drinking day) as compared to those with other variants of analyzed genes (N=230) (median 16.7, p=0.039) (Table 2). In addition, level of alcohol consumption was associated with family history of AD. Those who had alcohol-dependent relatives reported drinking more (median: 17.5 drinks per drinking day) than those who did not report AD in their family (median: 16.1 drinks, $p = 0.048$) (Table 3). There was no significant association between alcohol dependence in family and carrying both the *COMT* Met158Met genotype and *BDNF* Val66Val genotype. Among those with both genotypes (N=51), 35 participants reported AD in their family and 16 negated alcohol problems in family members. Among participants carrying other variants in the analyzed polymorphisms (N=230), 136 confirmed AD in family and 94 denied it. Differences were not statistically significant ($Chi^2 = 2.03$, $p = 0.15$).

All the analyzed parameters and factors were entered in the linear regression model, which was significant ($p<0.007$). In the model, only the co-occurrence of *COMT* Met158Met genotype and *BDNF* Val66Val genotype ($b = -3.91$, $p = 0.04$) and the family history of alcohol dependence ($b = -3.13$, $p = 0.04$) remained significant predictors of higher alcohol consumption (Table 4).

There was no statistically significant difference in the number of alcohol drinks consumed per drinking day in relation to being employed vs. unemployed (p=0.14), living alone vs. with the family (p=0.37), having kids vs. not having kids (p=0.19), and reporting enough money for living vs. those with serious economic disadvantage (p=0.11). Education level (p=0.28), age at onset of alcohol problems (p=0.10), and co-existing drug use (p=0.97) did not differentiate examined individuals in respect of alcohol consumption. Even attitudes of relatives – supporting sobriety or punishing and criticizing alcohol drinking – had no influence on how much alcohol was consumed by the participants during the average drinking day (p=0.26). Also, age of participants, gender, marital status or age of onset of alcohol problems were not correlated with level of alcohol consumption during the drinking day. Single *COMT* Met158Met or *BDNF* Val66Val genotypes separately were not associated with bigger alcohol intake. Only coexistence of those two genotypes was linked significantly to higher alcohol consumption.

Further analysis of characteristics of participants with the Met158Met genotype in the analyzed *COMT* polymorphism and Val66Val genotype in the *BDNF* polymorphism showed that they suffer from significantly more health problems (accordingly to general health scale from SF-36 inventory) (52.0 vs. 62.0, p=0.030), and have lower motivation to change drinking patterns as measured by the Socrates inventory (72.5 vs. 80.0 pts, $p = 0.031$) than those carrying other *BDNF* and *COMT* gene variants (Table 2).

1.4 Discussion

We analyzed factors that could be associated with the level of alcohol consumption in patients with alcohol dependence, with the expectation that economic status, employment or relatives' attitude might influence alcohol use. None of the social or demographic factors

was associated with the severity of alcohol consumption, but genetic factors and family history were independent correlates.

Since family history of alcohol dependence as well as the *COMT* Val158Met and *BDNF* Val66Met polymorphisms were the only factors associated with higher level of alcohol consumption in the study population, our data suggest that there might be a group of alcohol-dependent individuals with an inherited tendency to drink higher quantities of alcohol. Even though the mechanism remains unclear, the *COMT* and *BDNF* genes conceivably influence drinking patterns by their combined impact on the dopaminergic response to alcohol. Alcohol intoxication leads to dopamine release, which contributes to the rewarding effects of alcohol in the central nervous system. It is known that the *BDNF* Val66Val variant is linked to better functioning of dopaminergic neurons (Lee et al., 2013), possibly leading to higher dopamine release after alcohol intoxication. In addition, the *COMT* Met158Met variant results in expression of COMT with lower activity (Dumontheil et al., 2011), which leads to higher dopaminergic activity. Conceivably, therefore, alcohol drinking is more rewarding for patients with the combination of *BDNF* Val66Val and *COMT* Met158Met gene variants.

On the other hand, chronic alcohol use itself may result in disruptions of dopamine neurotransmission. We can expect that those changes together with *BDNF* Val66Val and *COMT* Met158Met variants can affect the level of alcohol consumption as well as motivation to drinking and mood regulation, but these relationships need further research.

Assuming that BDNF is a key regulator of the mesolimbic dopaminergic system, the effects of COMT on prefrontal dopaminergic catabolism might possibly be modulated by BDNF effects on dopamine release in the nucleus accumbens through the basal ganglia-thalamo-cortical pathway (Kang et al., 2013). These neurotransmitter and neurotrophin systems, which are involved in the different components of alcohol dependence, may be potential targets for the development of therapeutic agents for the treatment of alcoholism.

Limitations of the study

A limitation of our study is its cross-sectional design, not allowing for causal inferences. Another limitation is that only European Caucasians population was included in the analysis, thus the outcomes are not fully generalizable to the general population. We performed assessment of alcohol consumption only among individuals with alcohol dependence, thus limiting associations to individuals with generally high alcohol consumption. Data on alcohol consumption as well as those demographic and related to the relatives' attitude towards drinking were self-reported, what may cause possible bias due to subjective opinion of the participants of the study.

1.5 Conclusions

Patients carrying both the *BDNF* and *COMT* gene variants had significantly higher amounts of alcohol consumption, more health problems, and lower motivation to change drinking patterns. Accordingly, motivation-enhancing strategies might benefit this group of patients. Abstinence remains the optimal achievable goal in treatment of alcohol dependence;

however, some patients are unable to reach it. For those individuals, reduction of alcohol consumption may be a starting point for treatment. Reduction of alcohol intake could mitigate the risk of developing alcohol-related life-threatening diseases.

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Table 1

Distribution of genotypes and alleles in the *BDNF* Val66Met (rs6265) and *COMT* Val158Met (rs4680) polymorphisms.

Polymorphism	Genotype N (%)			Allele frequency		Chi-square *p-value*
	Val/Val	Val/Met	Met/Met	Val	Met	
BDNF (rs6265)	186 (66.4)	79 (28.1)	16 (5.5)	0.78	0.22	3.6 *0.06*
COMT (rs4680)	73 (25.9)	131 (46.6)	77 (27.5)	0.51	0.49	1.27 *0.258*

Table 2

Association between co-occurrence of *BDNF/COMT* genes variants and alcohol consumption, general health condition, and motivation to change drinking patterns

	Co-occurrence of *BDNF* Val66Val/ *COMT* Met158Met N = 51	***BDNF/COMT* Other variants N= 230**	***P* value**
Amount of alcohol per drinking day (number of standard drinks)[a]	19.3 (14.5; 26.0)	16.7 (12.2; 22.5)	0.039
General health condition (SF-36 health survey questionnaire)[a]	52.0 (35.0; 72.0)	62.0 (52.0; 72.0)	0.030
Motivation to change drinking patterns (SOCRATES)[a]	72.5 (62.0; 79.5)	80.0 (71.5; 86.5)	0.031

[a]Values represent medians and quartiles; Mann-Whitney test was used.

Table 3

Association between alcohol dependence in family and alcohol consumption

	Alcohol dependence among family members	**No alcohol dependence among family members**	***P* value**
Amount of alcohol per drinking day (number of standard drinks)[a]	17.5 (13.0; 25.0)	16.1 (11.9; 21.4)	0.048

[a]Values represent medians and quartiles; Mann-Whitney test was used.

Table 4

Correlates of alcohol consumption in linear regression analysis

	beta	*P* value
BDNF Val66Val / *COMT* Met158Met co-occurrence	−3.91	**0.04**
Alcohol dependence among family members (yes/no)	−3.13	**0.04**
Gender	−3.44	0.06
Age	0.02	0.76
Economic status	2.12	0.20
Employment (yes/no)	0.44	0.79
Age of onset of alcohol dependence	−0.12	0.22
Living alone (yes/no)	−0.19	0.91

R^2= 0.078; F(8,252)=2.66; p=0.008