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Original article

Polymorphism of *COMT* Val158Met is associated with inhalant use and dependence: a Thai substance dependence treatment cohort

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Background: Inhalants are abused by adolescents worldwide, but genetic markers of inhalant use or dependence are poorly understood.

Objective: We assessed the frequency and association of a functional polymorphism in the gene encoding catechol-O-methyltransferase (*COMT* Val158Met) in inhalant-dependent (ID) subjects and inhalant users (IU).

Methods: Demographic and diagnostic data were collected by interviewing 456 Thai-speaking methamphetamine (MA) users by using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). *COMT* Val158Met (rs4680) genotyping was acquired by restriction fragment length polymorphism. Individuals with ID or IU were compared with non-ID or non-IU by using a x^2 test. After that, factors associated with ID or IU were analyzed by logistic regression. Blood samples from 217 healthy blood donors were used as controls for ID and IU in the allele frequency comparison. Deviation from Hardy–Weinberg Equilibrium Expectations (HWEE) was also tested.

Results: Out of 456 MA users, deviation from HWEE was observed in IU but not in ID, non-ID or from the total sample. The "Met" allele was significantly associated with ID ($p = 0.02$) and IU ($p = 0.002$) among MA users, but not in allele frequency comparisons when compared to the healthy control group ($p > 0.1$). With respect to logistic regression analysis, homo or heterozygosity for the "Met" allele, male sex, younger age, lower level of education, a major depressive episode (MDE), and alcohol dependence were associated with ID. Analyses of IU vs. non-IU yielded the same results except for age and MDE. In addition, individuals with MA-induced paranoia (MIP) were more likely to have used inhalants at least once in their lifetime compared to those without.

Conclusion: *COMT* 158Met, male sex, younger age, lower level of education, MDE, MIP, and alcohol dependence increased risk for inhalant use and/or dependence.

Keywords: COMT, inhalant, methamphetamine, Thai, Val158Met

Volatile substances or inhalants, which are neurotoxic substances, are abused by adolescents worldwide because of their euphoric effect, easy accessibility (they are usually legal and inexpensive), and ease of use. Around 10% of adults in the U.S. have used inhalants at least once in their lifetime [1]. Common neurotoxic effects include, but are not limited to, impaired neurocognitive function (i.e., attention, memory) [2] and neuropsychiatric symptoms (i.e., psychosis) [3-5]. Chronic exposure to volatile substances causes a variety of forms of neuro-psychological cognitive impairment [2], particularly affecting the user's memory and prefrontal executive functions (such as poor attention) [6].

The pharmacodynamic effects of inhalants are still poorly understood, but like other central nervous system (CNS) depressants, it is believed that they involve the γ-aminobutyric acid (GABA) and

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glutamate systems [7]. Comprehensive clinical data and knowledge of the course of inhalant-use disorders are currently lacking despite the fact that their use is prevalent among adolescents [8-10], and they can be highly neurotoxic [2]. This is in contrast to the number of studies and data available for many other substance use disorders.

There has been limited research on the genetic markers associated with cognitive impairment and psychotic symptoms in inhalant users. One of the genes known to be associated with impaired prefrontal cognitive function and primary psychotic disorders is the catechol-O-methyl transferase gene (*COMT*), which is located on chromosome 22 and encodes a protein of 271 amino acids [11]. *COMT* Val158Met is a frequently-studied functional *COMT* polymorphism that results in substituting valine with methionine at codon 158 [12]. This Met variant has approximately 70% to 90% lower COMT activity than the Val variant [13] resulting in increasing levels of catecholamine activity [14]. *COMT* Val158Met has been reported to be related to a host of neuropsychiatric and substance dependence-related disorders and/or impairments, including interpersonal problem-solving in schizophrenic patients [15], reduced risk of psychotic features of bipolar disorder [16], and cocaine dependence [17].

In Thailand, inhalant use and dependence are on the rise, according to the reports issued in 2007 by the Administrative Committee of the Substance Abuse Academic Network [18]. This problem is currently affecting the future generation of workers and could impact increasingly high costs of long-term health care, which are burdens for the families involved as well as the taxpayers. In addition, there has been little research conducted in this population; most individuals abusing inhalants also abuse other illegal drugs, which further exacerbate their mental and physical health, and carries associated psychosocial and legal problems. Moreover, there are no data on the prevalence of *COMT* Val158Met in the Thai population. We therefore decided to study the association of *COMT* Val158Met with inhalant use-related disorders in Thai subjects.

Materials and methods

Subjects

Four hundred and fifty-six Thai-speaking, experienced methamphetamine (MA) users attending the Thanyarak Institute on Drug Abuse, a large inpatient drug dependence treatment center in Central Thailand, were recruited into the study between 2008 and 2010. Of 456 subjects, 136 were inhalant ever-users (IU) and 320 were non-IU. Forty-three were inhalant dependant (ID) and 413 were non-ID. All subjects were interviewed by using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA—Thai version) [19] as part of a MA-induced psychosis (n = 96), and alcohol dependence study. Inclusion and exclusion criteria have been described in detail elsewhere [20]. In addition, DNA samples were acquired from blood donors from the Thai Red Cross Society and were used as controls for individuals with ID and IU to assess the frequency of the *COMT* allele (see below). The race for the healthy controls did not match with the MA users; in the healthy control group, 18% of subjects were of Chinese descent (47 out of 264) whereas only 1% of MA users from Thanyarak Institute were of Chinese descent (5 out of 456), we therefore excluded 47 participants who were Chinese from the healthy control group. We were finally left with 217 healthy control subjects.

Because inhalants do not usually cause tolerance or withdrawal symptoms in users, we decided to expand our inclusion criteria to include those that have ever used inhalants, in this study also known as "IU". The decision to do this was based on results from several studies that investigated the phenotype of inhalant-dependent patients and showed differences between those that were dependant versus those that had ever used.

This study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University and the Ethics Committee of the Thanyarak Institute on Drug Abuse.

Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA)

The SSADDA is a comprehensive, psychiatric, interviewer-administered assessment with high overall inter-rater and test–retest reliabilities for substance dependence in both English (K = 0.59 and 0.80) [21] and Thai (K = 0.871, MA-induced paranoia (MIP); K = 0.97, opioid dependence versions) [19]. Five Thai-SSADDA interviewers, each with a clinical psychology degree, received extensive training before conducting the interviews. In this study, we used a quality-control protocol as previously described [19]. In brief, interviews were self-edited by the primary

interviewers for completeness and accuracy. Another independent pair of fully-trained interviewers would also check and edit the interviews. After the interviews were cross-edited, they were next reviewed and finalized by the primary interviewers. All interviews were approved by a Thai study physician qualified for the English version of SSADDA and were in the team that developed the Thai version of the SSADDA [19]. Interviews were reviewed monthly and group discussions of problematic interviews were conducted routinely for quality assurance.

Psychiatric diagnosis and substance use data from SSADDA interviews were scored using standard algorithms based on the Diagnostic and Statistical Manual for Mental Disorders version IV (DSM-IV). Demographic, diagnostic, and substance use data from 6 sections of the Thai SSADDA were used in the current study: Demographic Information (Section A), Tobacco (Section D), Alcohol (Section E), Methamphetamine (Section F—Cocaine in English version), Other Drugs (Section H), and Depression (Section J). Inhalant dependence (ID) was derived from the Other Drugs (Section H) of the SSADDA. Information of the participants' race was directly obtained from the questionnaire. Race was coded according to the grandparents' races. Specifically, having Thai race meant that having four Thai-grandparents (e.g., maternal grandparents and paternal grandparents were reported as Thais).

Genotyping COMT Val158Met

DNA was extracted from 10 ml of whole blood by means of a ZR Genomic DNA I Kit (Zymo Research, Irvine, CA). Each subject was genotyped for COMT Val158Met by PCR amplification followed by restriction endonuclease digestion. Val158Met region was amplified by using the following primers: 52 – TAGGGAGGGTGGGCAGAGGA–32 and 52–GACAACGGGTCAGGCATGCAC–32 (BioDesign, Pathumthani, Thailand). PCR reactions were carried out in a total final volume of 20 µl; PCR reaction was composed of 20 ng genomic DNA, 200 µM of dNTPs mix (Eppendorf, Hamburg, Germany), 0.05 µM of each reverse and forward primer, 1× PCR buffer and 0.1 U of Taq DNA polymerase (Qiagen, Valencia, CA). The amplification reaction was carried out with a preliminary denaturation at 95°C for 5 minutes followed by 35 cycles at 95°C for 30 seconds, 65°C for 30 seconds, and 72°C for 30 seconds. The lengths of the PCR products were 363 bp. After obtaining the PCR products, they were digested using 10 U of *Nla*III in 1 × NE Buffer 4 and BSA (New England BioLabs, Beverly, MA) overnight at 37°C. The digested products of the Met allele were visualized using an 8% acrylamide gel. The Met allele was identified by 4 fragments with the following sizes: 235, 96, 18, and 14 bps. The Val allele was identified by 3 fragments with the following sizes: 235, 114, and 14 bps.

Statistical analysis

Non-normally distributed continuous-variables were transformed into categorical data. *COMT* Val/Met and Met/Met genotypes were combined into one group for statistical purposes. We conducted statistical analysis in an exploratory manner to study independent risk factors for ID. First, all gene and environmental data (i.e., demographics, major depressive episode, other substance dependencies) were analyzed by using two-tailed $\div^2$ tests to investigate associations with ID. After that, backward elimination logistic regression analysis was applied to variables associated with ID at a significant ($p < 0.05$) or trend-level ($p < 0.1$). Race (e.g., being Thai and others) was also entered in the final model for logistic regression analysis to control for population bias. Potential differences in allele frequency between ID and non-ID in MA users and ID and healthy controls were assessed using a x^2 test. Consistency with Hardy–Weinberg Equilibrium Expectations (HWEE) was ascertained. In addition, analyses identical to those described above were done for IU. All statistical analysis was performed by using SPSS version 16.

Results

Risk factors for ID

Out of 456 MA using subjects, 43 (9.4%) met the DSM-IV diagnostic criteria for ID. Individuals with ID were more likely to be male (x^2 = 7.8, df .= 1, p = 0.005), younger (x^2 = 9.1, df = 1, p = 0.003), have lower levels of education (x^2 = 7.6, df = 1, p = 0.006), have a history of major depressive episode (x^2 = 9.9, df = 1, p = 0.002), and be dependent upon other substances (e.g., nicotine (x^2 = 8.0, df = 1, p = 0.005) and alcohol (x^2 = 7.1, df = 1, p = 0.008)). Other demographic variables (i.e., race, marital status, employment, household gross income) and diagnoses (e.g., MA-induced paranoia or MIP) were not different between groups (p >0.05) (**Table 1**).

Table 1. Demographics and diagnoses of individuals with and without inhalant dependence (ID)

	ID (n = 43) n (%)	Non-ID (n = 43) n (%)	x^2	*p* values
Sex				
Male	32 (74.4)	215 (52.1)	7.8	0.005**
Female	11 (25.6)	198 (47.9)		
Race[a]				
Thai	32 (74.4)	285 (69.0)	0.5	0.463
Others	11 (25.6)	128 (31.0)		
Age (years)				
18-21	19 (44.2)	96 (23.2)	9.1	0.003**
≥22	24 (55.8)	317 (76.8)		
Level of education (years)				
<9	30 (69.8)	197 (47.7)	7.6	0.006**
≥9	13 (30.2)	216 (52.3)		
Marital status				
Widow, separated, divorced	4 (9.3)	60 (14.5)	3.9	0.142
Never married	38 (88.4)	313 (75.8)		
Married	1 (2.3)	40 (9.7)		
Household income (baht/month; 1 US$ = 30 baht)				
0-10,000	16 (37.2)	154 (37.3)	1.4	0.507
10,001-20,000	11 (25.6)	136(32.9)		
≥20,001	16 (37.2)	123 (29.8)		
Unemployment	35 (81.4)	351 (85.0)	0.4	0.534
Major depressive episode	12 (27.9)	46 (11.1)	9.9	0.002**
Nicotine dependence	36 (83.7)	256 (62.0)	8.0	0.005**
Alcohol dependence	21 (48.8)	120 (29.1)	7.1	0.008**
Methamphetamine dependence	36 (83.7)	322 (78.0)	0.8	0.382
Methamphetamine-induced paranoia	15 (34.9)	142 (34.4)	0.004	0.948

*$p < 0.05$, **$p < 0.01$, [a]Thai ethnicity was determined by self-report. These participants had all Thai grandparents. Other races included Chinese (n = 5), Thai-Chinese (n = 66), Thai with other races (n = 34), and Thai with unknown races (n = 34).

With respect to *COMT* genotypes, individuals with ID were more frequently heterozygous or homozygous for the Met allele in comparison to non-ID ($x^2 = 7.7$, df = 2, $p = 0.02$). Similarly, with respect to allele frequency, there was a higher frequency of Met alleles in individuals with ID compared to non-ID ($p = 0.02$) (**Table 2**). However, individuals with ID did not differ from the healthy controls (i.e., sample from blood donors) with respect to the frequency of the allele (0.37 vs. 0.31, respectively; $x^2 = 1.4$, df = 1, $p = 0.23$). Frequencies of the allele in ID, non-ID or combined sample were in HWEE.

Table 2. Frequencies and types of *COMT* Val158Met polymorphisms among study population

	***COMT* genotypes**				***COMT* alleles**		
	Val/Val n (%)	Met/Val n (%)	Met/Met n (%)	*p* values	Valn (%)	Metn (%)	*p* values
Inhalant dependence (ID)							
ID (n = 43)	15 (34.9)	24 (55.8)	4 (9.3)	0.02*	54 (62.8)	32 (37.2)	0.02*
Non-ID (n = 413)	234 (56.7)	147 (35.6)	32 (7.8)		615 (74.5)	211 (25.5)	
Inhalant ever-use (IU)							
IU (n = 136)	61 (44.9)	59 (43.4)	16 (11.8)	0.01*	181 (66.5)	91 (33.5)	0.002**
Non-IU (n = 320)	188 (58.8)	112 (35.0)	20 (6.2)		488 (76.2)	152 (23.7)	

*$p < 0.05$, **$p < 0.01$

From the logistic regression analysis (backward likelihood ratio), *COMT* Val158Met was associated with ID. Individuals who were either heterozygous or homozygous for the Met allele were at 2.4 times greater risk of being dependent upon inhalants (p = 0.01, df = 1, odds ratio (OR) = 2.4). Other risk factors predictive for ID were male sex (p = 0.008, df = 1, OR = 2.8), younger age (p = 0.004, df = 1, OR = 2.8), and lower levels of education (p = 0.001, df = 1, OR = 3.5). Major depressive episode (MDE) (p = 0.003, df = 1, OR = 3.4) and alcohol dependence (p = 0.010, df = 1, OR = 2.5) were also associated with ID (**Table 3**).

Risk factors for IU

Out of 456 MA using subjects, 136 (29.8%) intentionally used inhalants for recreational purposes at least once in their lifetime (i.e., so-called inhalant ever-use (IU). Sex (x^2 = 14.2, df = 1, p < 0.001), level of education (x^2 = 20.8, df = 1, p < 0.001), nicotine dependence (x^2 = 6.5, df = 1, p = 0.01), alcohol dependence (x^2 = 21.5, df = 1, p < 0.001), and MIP (^{2} = 8.1, df = 1, p = 0.005) distinguished IUs from non-IUs. Major depressive episode was nearly significantly associated with IU (p = 0.08). With respect to genetic variables, IU was associated with a higher frequency of heterozygosity or homozygosity for Met as compared to non-IU (x^2 = 8.8, df = 2, p = 0.01). Similar results were also obtained from allele frequency analysis (p = 0.002). However, individuals with IU did not differ from the healthy controls in respect to the frequency of the allele (0.33 vs. 0.31, respectively; x^2 = 0.6, df = 1, p = 0.44). Allele frequency in IU was not in HWEE.

From the logistic regression analysis, risk factors for IU were Met mutations in the *COMT* gene (p = 0.02, df = 1, OR = 1.7), male (p < 0.001, df = 1, OR = 2.7), lower levels of education (p < 0.001, df = 1, OR = 3.4), alcohol dependence (p < 0.001, df = 1, OR = 2.5) and MIP (p = 0.03, df = 1, OR = 1.6).

Table 3. Genetic and environmental risk factors for inhalant dependents analyzed by logistic regression analysis

	Wald	df	Odds ratio	*p* values	95% Confidence interval	
					Lower	Upper
***COMT* Val158Met**						
Met/Met and Met/Val	6.1	1	2.4	0.013*	1.2	4.8
Val/Val						
Sex						
Male	7.0	1	2.8	0.008**	1.3	6.1
Female						
Age (years)						
18–21	8.5	1	2.9	0.004**	1.4	5.8
≥22						
Level of education (years)						
<9	10.6	1	3.5	0.001**	1.6	7.4
≥9						
Major depressive episode						
Yes	8.9	1	3.4	0.003**	1.5	7.5
No						
Alcohol dependence						
Yes	6.6	1	2.5	0.010**	1.2	5.1
No						
Races						
Thai	0.0	1	1.0	0.985	0.5	2.2
Others						

*p < 0.05, **p < 0.01, Wald: Wald test, df: degree of freedom

Discussion

In comparison with other age groups, inhalants are popular among teenagers around the world [22]. Their ease of use, affordability and availability may explain why teenagers start experimenting with inhalant substances and some of them eventually become frequent users [23]. In these groups, cognitive and prefrontal executive functions are damaged, in part presumably because the volatile substances increase the release of dopamine (DA) in the nucleus accumbens by stimulating VTA DA neurons [24].

The effects of DA have been shown in both animal and human models [25, 26] to contribute to the development of substance abuse and dependence through the brain reward circuit [27]. Various substance-related behaviors have previously been reported to be associated with COMT genotype. COMT degrades catecholamines such as DA and norepinephrine (NE) in the prefrontal cortex [28] whereas the 158Met allele of COMT has been shown to enhance cognitive function [29] and protect cognitive impairment, especially for the memory and executive functions of the brain [30]. To our knowledge, this study is the first to report an association between a genetic marker and use and dependence on inhalants. In our study population, there were 30% IU and 9% ID among experienced MA users. From both the uni- and multi-variate analyses, heterozygosity and homozygosity for Met alleles and lower educational levels were significantly associated with IU and ID. This finding is consistent with other reports for educational level for substance dependents [31]. While we do not know whether there is a link between cognitive function and level of education in IU and ID, we did observe that individuals with ID had a lower educational level and a higher proportion of the 158Met allele, presumably a higher cognitive function allele. Because of this, cognitive function alone may not explain ID, nor can we assume the two to be associated with one another. Therefore, we cannot conclude that the link between 158Met allele and IU/ID is associated with cognitive function. Other demographic variables (i.e., male, young age) were also associated with IU or ID. These data are consistent with reports issued by the U.S. National Survey on the Characteristics of Inhalant Users [22]. We observed that males had a higher risk for IU/ID compared to females. We speculate that this is due to societal and cultural differences or perhaps biological differences between males and females. Another significant risk factor for ID was depression. This is not surprising since many primary psychiatric disorders (i.e., anxiety, depression, and even psychotic disorders) are known to be associated with substance dependence [32, 33]. Moreover, paranoia under the influence of MA was associated with IU. This is consistent with the results from a smaller (and overlapping) study [20]. There are two possible explanations for this. First, inhalants may have increased the propensity for paranoia when MA is used through pro-psychotic dopaminergic mechanisms. However, this is unlikely because it would imply that MIP should be increased in the ID group as well, which was not the case. Another possible explanation could be that paranoia is simply an adverse effect of MA and inhalants have attenuated this effect. This explanation is more plausible and therefore we have concluded that inhalants may be used to alleviate the aversive effects of MA.

Our study has several limitations. For instance, we did not include those who were severe inhalant users (i.e., those with daily use) in the ID group because they did not meet the criteria for DSM-IV dependence. It is very difficult to diagnose ID despite compulsive use given the clinical paucity of symptoms of withdrawal or tolerance. Second, in this study, we only examined for one marker of *COMT*. We did not investigate other markers within the gene; however, we selected only the functional one that would predict up to 70% to 90% of the COMT activity. Third, our sample size is small compared with previous genetic studies of substance dependence, and therefore, the possibility of a type-II error should be considered. Fourth, all of our subjects were dependent on other drugs, which could have inadvertently affected the results (i.e., the current sample was a clinical sample of convenience, and not an epidemiological one). In our area, individuals who exclusively use and/or are dependent upon on inhalants are uncommon. However, our healthy controls for ID and IU were non-drug users. We detected no differences in allele frequency between case and controls. It is possible that we were unable to detect any differences between the groups because the race of the participants could have negatively confounded the results. We tried to minimize this confounding factor by excluding participants of Chinese descent from the healthy control group to maintain a more homogeneous sample. Yet this healthy control sample still contained a modest proportion of Thais mixed with other races.

Similarly, the association between *COMT* 158Met and ID or IU in MA users may be a false positive that has resulted from this population bias. In our study, we excluded individuals younger than 18 years of age because of legal issues. Therefore, this data should be interpreted with caution, because it is possible that teenagers under 18 years of age may have different risk factors for ID and IU than the ones reported.

Future studies in participants younger than 18 years are recommended. Such data will be important because a majority of IU and ID are in this age group. Second, other genes that target the production, elimination and expression of DA and/or its receptors should be investigated for their association with inhalant use/disorders. Third, studies should also include severe, asymptomatic inhalant users and to be more thorough when examining these groups of people. Last, a purer sample population, homogeneous participants that are not dependant on other substances, is needed to confirm our findings in a larger study.

Conclusion

In our study, *COMT* Val158Met was found to be a risk factors for ID and IU. In addition, environmental factors such as sex, age, level of education, major depressive episode, and alcohol dependence are also implicated in inhalant-use disorder. These findings may help us understand and ultimately prevent future IU and ID; parents should keep these risk factors in mind when they are dealing with adolescents.

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