A Meta-Analysis for Understanding the Role of the COMT Val158Met Variant in the Susceptibility to Alcoholism

Authors

Deeplata Barman[1], Mohan Krishna Ghanta[2], Sagar Jangde[1], Babul Meher[1], Nisha Sahu[1] and LVKS Bhaskar[1]

Affiliations

[1]Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur

[2]Department of Pharmacology, MVJ Medical College and Research Hospital, Bangalore

***Corresponding author**

LVKS Bhaskar

E-mail: lvksbhaskar@gmail.com

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ABSTRACT

The hypothesis of association between 158Met allele of catechol-o-methyltransferase (COMT) gene and poor dopamine catabolism, dopamine remains prolonged for their half-time in the prefrontal cortex and gets more reward from alcohol than COMT Val158 allele, has generated much interest, research and controversy. Hence, a meta-analysis to explore possible role of COMT Val158Met variant and alcoholism has been performed. Twenty-two case-control data sets containing 3602 alcoholism patients and 5183 healthy subjects genotyped for COMT Val158Met variant has been included and assessed for their association with alcoholism. Meta-analyses were conducted with the use of MetaGenyo web tool. The results of this study confirmed that the COMT Val158Met variant is not contributing to the risk of alcoholism (Dominant model: OR = 1.10 (95% CI = 0.92-1.30), I^2 = 49%). Subgroup analysis by ethnicity also found no association of this allele with alcoholism risk in both Asian (Dominant model: OR = 1.15 (95% CI = 0.83-1.60), I^2 = 43%) and Caucasian (Dominant model: OR = 1.07 (95% CI = 0.87-1.32), I^2 = 54%) populations. The meta-analysis results of this study suggest no significant correlation between COMT Val158Met variant and alcoholism.

Keywords: *Alcoholism, dopamine, COMT, Val158Met, meta-analysis*

INTRODUCTION

Alcoholism continues to be a social and economic problem, resulting in three million deaths worldwide each year (Lim et al., 2012; Organization, 2019). Alcohol is a psychoactive substance that can penetrate the blood-brain barrier to enter the brain, and alter neurotransmitters, leading to aberrant brain activity and associated behaviors (Hipólito et al., 2007). Alcohol's behavior is biphasic in nature, as increased blood alcohol levels increase stimulant properties and decreased levels causes depressant properties (Li et al., 2020). At high doses, alcohol decreases bilayer characteristics and stability leading to increased ion permeability and cell toxicity manifesting in

multiorgan damage and organ failure (Osna and Kharbanda, 2016). Alcohol consumption enhances ventral tegmental dopamine secretion in the nucleus accumbens (NAc) and produce pleasurable effects culminating into reinforcing behaviors (Bhaskar and Kumar, 2014). Even a small dosage alcohol consumption, causes the NAc to release more dopamine, which has an impact on the reward system that favors the motivational cues to repeat alcohol use (Di Chiara, 1997). The dopaminergic pathway includes a complex set of sequential events such as production of dopamine, storage, secretion, receptor transduction, re-uptake, as well as breakdown of dopamine by specific enzymes.

Catechol-O-methyltransferase (COMT), an extra-neuronal enzyme, catabolizes dopamine, norepinephrine, as well as epinephrine via a transmethylation reaction (Männistö and Kaakkola, 1999). The gene for COMT is located on the long arm of chromosome 22 (22q11), and encoding membrane bound (MB-COMT) and soluble (S-COMT) isoforms (Tenhunen et al., 1994). Translocation of G to A at 158 codon substitutes methionine (158Met) to valine (Val158) in MB-COMT transcript (Lachman et al., 1996). The 158Met allele has been linked to decreased COMT activity and less thermolabile in contrast to Val158 allele. Thus, the carriers of Val158 allele catabolizes three to four times of dopamine than the carriers of 158Met allele. As the carriers of met allele involved in poor dopamine catabolism, dopamine remains prolonged for their half-time in the prefrontal cortex and gets more reward from alcohol than normal. As a result, COMT Val158Met variant was a considered biomarkers of multiple psychiatric disorders including alcoholism. Till date, COMT Val158Met variant and alcoholism risk association was inconclusive, irrespective of several research (Altintoprak et al., 2012; Choi et al., 2006; Czarnecki et al., 2021; Enoch et al., 2006; Hallikainen et al., 2000; Ishiguro et al., 1999; Köhnke et al., 2003; Kweon et al., 2005; Liu et al., 2005; Malhotra et al., 2016; Nakamura et al., 2001; Nikolac et al., 2013; Samochowiec et al., 2008b; Schellekens et al., 2012; Serý et al., 2006; Singh et al., 2017; Soyka et al., 2015; Voisey et al., 2011; Wang et al., 2011; Zhang et al., 2013).

The study aimed at establishing the relationship between COMT Val158Met variant and alcoholism using a meta-analysis approach.

METHODS

The PubMed Web of Science and Google Scholar databases were searched for pertinent papers published before May 1st, 2023. The following keywords and MeSH terms were used: [“Alcoholism” or “Alcohol dependence”] and [“catechol-O-methyltransferase” or “COMT”] and [“rs4680” or “Val158Met”]. Further manual search of the reference lists from the relevant articles was performed to find other potential articles. Case-control studies that focused on the association of COMT Val158Met polymorphism with the alcoholism with sufficient information about the genotype

frequencies were included in the meta-analysis. Two researchers independently collected the following data from each paper: year of publication, the first author, geographical location, sample size, genotyping method, source of the control, genotype frequencies, etc. The data extracted from all included studies was tabulated (Table 1). MetaGenyo web application was used for meta-analysis. Crude odds ratios (ORs) with their 95% confidence intervals (95%CI) were calculated to evaluate their relationships under dominant, recessive and allelic models. The Cochran's Q-statistic and I^2 test were used to evaluate potential heterogeneity between studies. As significant heterogeneity was found between studies (Q-test $P<0.05$; I^2 = 49%) a random-effect model was for calculating pooled ORs. Subgroup analyses by ethnicity was conducted to investigate potential sources of heterogeneity. A sensitivity analysis was conducted by leaving one study at a time, to assess the influence of single studies on the overall ORs. Publication bias was assessed using Begg's funnel plots and Egger's linear regression test.

RESULTS

A PRISMA flow diagram depicting the selection process of eligible articles is shown in figure 1. Twenty-two case-control studies with a total of 3602 Alcoholism patients and 5183 healthy subjects met our inclusion criteria for qualitative data analysis. Overall, 13 studies were conducted among Caucasians and only nine studies were performed among Asians. Five genotyping methods were used in these studies, including PCR-RFLP, TaqMan assay, PCR-Melt curve, Sequenom MassARRAY, and Illumina® SNP Genotyping methods. Meta-analysis findings on the Association of COMT Val158Met polymorphism and risk of developing alcoholism in different genetic models were shown in table 2. The results of our meta-analysis suggested that COMT Val158Met polymorphism is not associated with an increased risk of alcoholism (allele model: OR =1.05, 95% CI: 0.95□1.17, p=0.342; dominant model: OR=1.10, 95%CI: 0.92□1.30, p=0.302; recessive model: OR=1.04, 95%CI: 0.90□1.21, p=0.570; respectively) (Figure 2). Among different ethnic subgroups, the results demonstrated that the Val158Met polymorphism is not associated with increased risk of alcoholism among both Asians and Caucasians (Table 2). The results of the sensitivity analysis demonstrated that individual studies could not influence the overall pooled ORs (Figure 3). Symmetry in the Begg's funnel plots indicates no publication bias (Figure 4). Egger's test also revealed no publication bias (all $p>0.05$).

Figure 1: PRISMA checklist for identifying the papers to include in the meta-analysis.

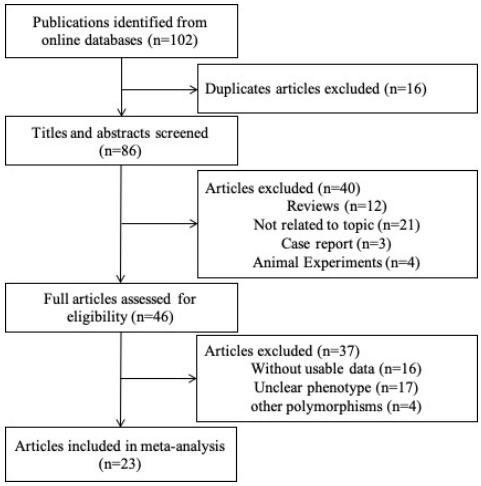

Figure 2: Forest plot summarising a meta-analysis of alcoholism and COMT Val-158Met using dominant genetic model.

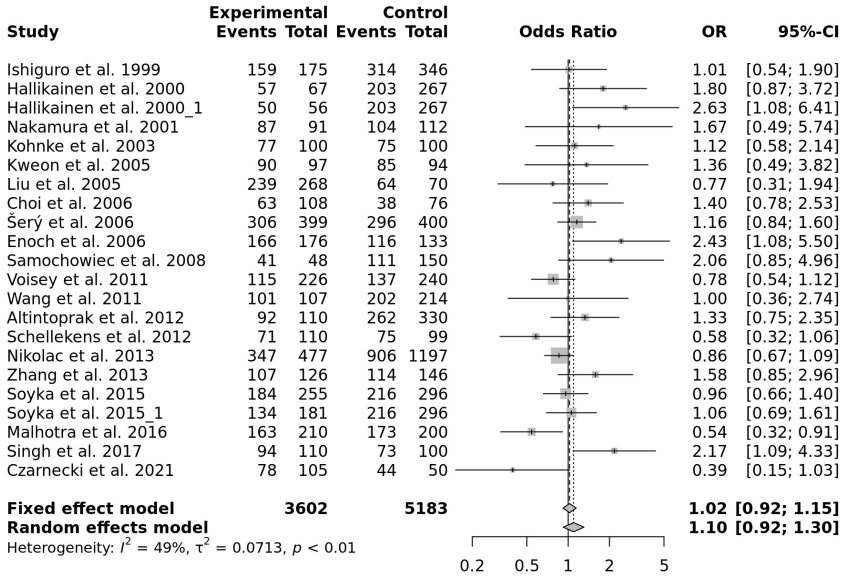

Figure 3: Forest plot of "leave-one-out" sensitivity analysis method.

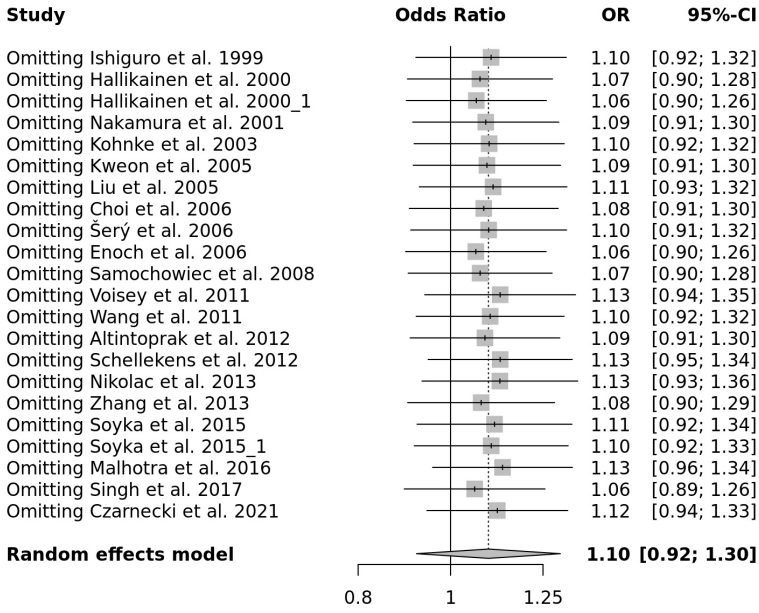

Figure 4: Begg's funnel plot for publication bias tests.

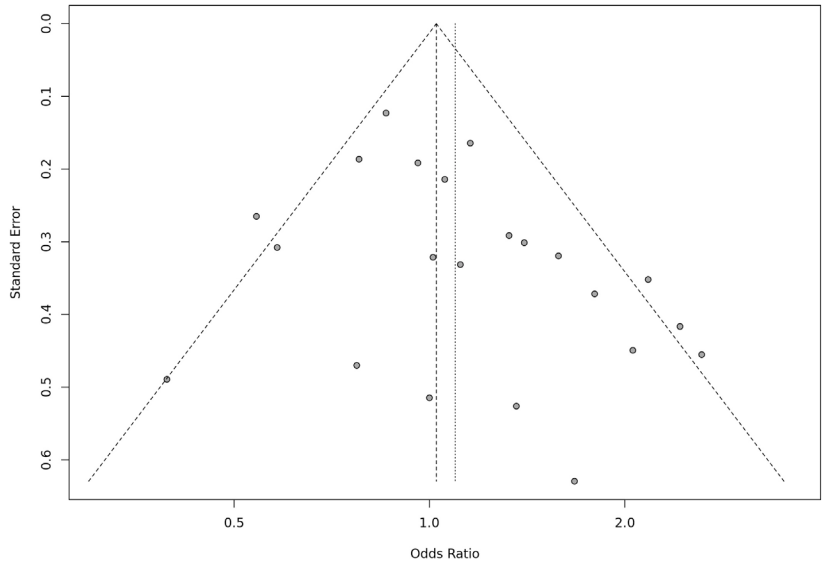

Table 1: Characteristics of studies included in the meta-analysis and distribution of genotypes of the COMT Val158Met polymorphism.

Study Reference	Year of publication	Ethnicity	Country	Genotyping Method	Alcoholism			Controls		
					Met/Met	Met/Val	Val/Val	Met/Met	Met/Val	Val/Val
Altintoprak et al.	2012	Asian	Turkey	PCR-RFLP	47	45	18	137	125	68
Enoch et al.	2006	Caucasian	USA	Taqman-Assay	91	75	10	59	57	17
Voisey et al	2011	Caucasian	Australia	RT-PCR	18	97	111	39	98	103
Hallikainen et al.	2000	Caucasian	Finland (Turku)	PCR-RFLP	22	35	10	67	136	64
Hallikainen et al.	2000	Caucasian	Finland (Kuopio)	PCR-RFLP	20	30	6	67	136	64
Ishiguro et al.	1999	Asian	Japan	PCR-RFLP	85	74	16	166	148	32
Kweon et al.	2005	Asian	Korea	PCR	54	36	7	47	38	9
Liu et al.	2005	Asian	Japan	Mass Array	115	124	29	40	24	6
Malhotra et al.	2016	Asian	India	RT-PCR	51	112	47	64	109	27
Nakamura et al.	2001	Asian	Japan	PCR	45	42	4	49	55	8
Nikolac et al.	2013	Caucasian	Croatia	Taqman-Assay	117	230	130	289	617	291
Samochowiec et al.	2008	Caucasian	Poland	PCR	20	21	7	42	69	39
Schellekens et al.	2012	Caucasian	Netherlands	Taqman-Assay	26	45	39	22	53	24
Šerý et al.	2006	Caucasian	Czech	PCR-RFLP	107	199	93	93	203	104
Soyka et al.	2015	Caucasian	German	PCR	57	127	71	67	149	80
Soyka et al.	2015	Caucasian	Poland	PCR	48	86	47	67	149	80
Zhang et al.	2013	Asian	China	Array based method	41	66	19	41	73	32
Singh et al.	2017	Asian	India	PCR	31	63	16	31	42	27
Czarnecki et al.	2021	Caucasian	Poland	RT-PCR	21	57	27	20	24	6

Choi et al.	2006	Asian	korea	PCR	17	46	45	4	34	38
Wang et al.	2011	Asian	China	PCR-RFLP	61	40	6	106	96	12
Köhnke et al.	2003	Caucasian	Germany	PCR	27	50	23	32	43	25

Table 2: Pooled results from meta-analysis by ethnicity.

Genetics model	Ethnicity	Model	No. of studies	Test of Association		Het-eroge-neity I^2	Egger's test p-value
				OR(95% CI)	p-val		
Allele Model (Met vs. Val)	Overall	Random	22	1.05 (0.95-1.17)	0.342	59%	0.306
	Asian	Random	9	1.07 (0.89-1.28)	0.495	55%	0.161
	Caucasian	Random	13	1.05 (0.91-1.20)	0.511	64%	0.579
Recessive model (Met/Met vs. Met/Val + Val/Val)	Overall	Random	22	1.04 (0.90-1.21)	0.570	48%	0.906
	Asian	Random	9	1.03 (0.81-1.32)	0.797	49%	0.218
	Caucasian	Random	13	1.05 (0.87-1.27)	0.603	52%	0.625
Dominant model (Met/Met + Met/Val vs. Val/Val)	Overall	Random	22	1.10 (0.92-1.30)	0.302	49%	0.073
	Asian	Random	9	1.15 (0.83-1.60)	0.407	43%	0.464
	Caucasian	Random	13	1.07 (0.87-1.32)	0.512	54%	0.139

DISCUSSION

Some studies reported an association between the COMT Val158Met variant and the risk of alcoholism, while others found no such association. To help resolve these contradictory outcomes, we conducted a meta-analysis. In this review, we included 26 studies investigating the association of COMT Val158Met variant and the alcoholism risk. We found that the COMT Val158Met variant is not contributing to the risk of alcoholism in both Asian and Caucasian populations. As is known, the 158Met allele may have reduced activity level of COMT enzyme, thereby affecting dopamine catabolism leading to greater extra synaptic dopamine build-up. Similar COMT Val158Met allelic distribution patterns couldn't reveals significant association of COMT gene with alcoholism among Japanese population (Ishiguro et al., 1999). In contrast, American Indian alcoholics carried not less than one extra Val158 allele compared to non-alcoholics (Enoch et al., 2006). While in Czech population, significant association was found with COMT Val158 allele to alcoholism in male population and, female population did not exhibit any association, opening doors to gender variations for further evaluation (Serý et al., 2006). Subsequent case control and family-based association studies in samples of European populations couldn't establish any relationship of alcoholism to COMT (Foroud et al., 2007; Samochowiec et al., 2006). Also, there existed no relation with Lesch types of alcoholics to COMT Val158Met alleles (Samochowiec et al., 2008). A previous meta-analysis of six Asian and twelve Caucasian studies couldn't establish COMT Val158Met as a risk factor of alcoholism (Chaudhary et al., 2021). Another meta-analysis of 18 case-control studies and two cohort studies also found that the COMT Val158Met variant is not associated with alcohol use disorders (Jin and Zhao, 2020). Although, many independent association studies and meta-analyses indicated that the COMT Val158Met is not contributing to the risk of alcoholism, the relapse rate is high in patients carrying 158Met allele compared to those lacking this allele (Wojnar et al., 2009). Further, among Russian alcoholic population, those who had a family history of alcoholism exhibited high incidence of 158Met allele (Kibitov et al., 2010). Furthermore, a study assessing the alcohol craving severity and COMT polymorphism relationship, indicated that this polymorphism may not have a direct link to alcohol craving intensity throughout the abstinence (Czarnecki et al., 2021).

CONCLUSION

The results of this meta-analytic study suggest that, the COMT Val158Met variant is not contributing to the risk of alcoholism in both Asian and Caucasian populations. As alcoholism is a complex disorder, type of alcoholism, geographic location, environmental conditions and criteria used for phenotyping needs to be considered in future studies, together with consideration of interaction with multiple genes involved in the dopaminergic pathway.

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