Lack of Association between rs4680 Polymorphism in Catechol-O-Methyltransferase Gene and Alcohol Use Disorder: A Meta-Analysis

Xin-Rong Jin and Zhi-Qiang Zhao

Xinjiang Mental Health Center and Urumqi Fourth People’s Hospital, Urumqi 830002, China

Correspondence should be addressed to Xin-Rong Jin; jxr791020@163.com

Received 11 June 2020; Revised 8 October 2020; Accepted 23 October 2020; Published 17 November 2020

Academic Editor: Michele Malaguarnera

Copyright © 2020 Xin-Rong Jin and Zhi-Qiang Zhao. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. The underlying mechanisms of alcohol use disorder (AUD) are regarded to be strongly associated with genetic factors. Although great efforts have been made to identify the association of rs4680 polymorphism in the catechol-o-methyltransferase gene and risk to AUD, the outcomes were still inconsistent. This study is aimed at exploring the association of rs4680 polymorphism and AUD by using a meta-analysis approach.

Methods. Literature searching was undertaken across PubMed, Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases. We set the search period before February 20, 2020. We used the Review Manager 5.3 (RevMan 5.3) software to estimate the effect sizes in five genetic models.

Results. In total, eighteen case-control studies and two cohort studies were included in this study. The merged results of overall population indicated there was no significant association between rs4680 polymorphism and AUD: V vs. M, OR = 1.02, 95% CI 0.93-1.12, P = 0.70; VV vs. MM, OR = 0.99, 95% CI 0.79-1.23, P = 0.92; VM vs. MM, OR = 0.91, 95% CI 0.81-1.03, P = 0.15; VV+VM vs. MM, OR = 0.95, 95% CI 0.80-1.13, P = 0.65; VM vs. MM+MM, OR = 1.04, 95% CI 0.91-1.18, P = 0.57. Subgroup analysis by gender suggested rs4680 polymorphism was marginally associated with an elevated risk to AUD among males (VM vs. MM, OR = 0.81, 95% CI 0.67-0.98, P = 0.03). However, subgroup analysis by race and diagnosis did not support any significant association.

Conclusions. The present study suggests that rs4680 polymorphism has no association with AUD in the overall population, but it has a weak association with AUD in males. Carriers of VM genotype in males appear to have an increased risk to AUD.

1. Introduction

Alcohol use disorder (AUD) is a chronic relapsing psychiatric disorder manifested by excessive alcohol consumption, which often results in physical and psychological symptoms [1]. Obsessive and compulsive use of alcohol is widely seen in various countries and ethnicities. Statistics from the World Health Organization (WHO) displayed that about 3 million people die from alcohol-related diseases every year. About 3.8% of global deaths and 4.6% of global disability-adjusted life years lost are caused by excessive alcohol consumption, thus leading to enormous economic burden and huge health problems [2]. Despite all these efforts on the study of AUD have been made in recent years, the exact etiology and pathogenesis of AUD are yet an unanswered question. Therefore, the investigation of the underlying molecular mechanisms of AUD may help us explore preventive and treatment measures.

Evidence in many studies showed that more than 50% of the risk factor could be attributed to genetic components [3, 4]. The association of Val158Met (rs4680) polymorphism in catechol-O-methyltransferase (COMT) and AUD was first investigated by a Japanese study [5]. Another study published in 2004 indicated that rs4680 polymorphism has a significant influence on enzyme activity, the enzyme activity of COMT-Met is about 40% lower than that of COMT-Val in human
dorsolateral prefrontal cortex at normal physiological temperature [6], and this may influence neurotransmitters dopamine, epinephrine, and norepinephrine signaling.

COMT is a protein-coding gene located on human chromosome 22q11.2. Its classical function is to catalyze the transfer of methyl groups from S-adenosylmethionine to catecholamines. This O-methylation leads to the major degradative pathway of the catecholamine transmitters and thus regulates the metabolisms of neurotransmitters dopamine, epinephrine, and norepinephrine. Polymorphisms in COMT may alter its expression level and enzyme activity. The past several decades have seen numerous investigations about the association of rs4680 polymorphisms in COMT and the risk of AUD, but their results are inconsistent. Therefore, the present work is aimed at providing a comprehensive analysis of individual studies and elucidating the correlation of rs4680 polymorphism and AUD susceptibility.

2. Methods

2.1. Literature Search. We searched Web of Science, PubMed, Embase, Wanfang, and CNKI databases. The search string was (Polymorphism OR SNPs OR Mutant OR Variant OR “Polymorphism, Single Nucleotide”[Mesh]) AND (Alcohol Dependence OR Alcohol Addiction OR Chronic Alcoholic Intoxication OR Alcohol Use Disorder OR Alcohol Use Disorders OR Alcohol Abuse OR Alcohol misuse OR Problem drinking OR Harmful drinking OR Alcoholics OR Alcoholism) AND (Catechol-O-Methyltransferase OR Catechol O Methyltransferase OR Catechol Methyltransferase OR COMT OR Catecholamine-O-methyltransferase OR Val108/158Met OR rs4680 OR "Catechol O-Methyltransferase"[Mesh]). Language restriction was not posed. The latest search was performed on February 20, 2020.

2.2. Inclusion and Exclusion Criteria. Studies that met the following criteria were included: (1) case-control or cohort studies on rs4680 polymorphism and AUD; (2) studies with available data for calculating odds ratio (OR) and 95% confidence interval (95% CI). Letters, editorials, duplicate studies, and case reports were excluded. All studies were reviewed by two investigators independently. Any discrepancy was resolved by mutual consent.

2.3. Data Extraction and Quality Assessment. Two investigators abstracted main information from the eligible studies: author’s name, publication year, nation, ethnicity, gender, design, diagnostic criteria, sample size, genotype and/or allele distribution, and results of the Hardy-Weinberg equilibrium (HWE) test [7]. The quality of eligible studies was evaluated based on the Newcastle-Ottawa Scale (NOS). The NOS contained eight items, which were categorized into three boards including selection, comparability, and exposure. The studies with five or more scores were considered to be in high quality. Discrepancies were addressed by mutual consent.

2.4. Statistical Analysis. ORs together with 95% CIs were calculated to appraise the association of rs4680 polymorphism and alcohol use disorder under five genetic models including allelic model (V vs. M), homozygous model (VV vs. MM), heterozygous model (VM vs. MM), dominant model (VV + VM vs. MM), and recessive model (VV vs. VM+MM). We used the Q-statistical test and $I^2$ test to check the between-study heterogeneity. In the condition of $P < 0.1$, $I^2 > 50\%$, the random-effects model was selected. Otherwise, the fixed-effects model was used. Subgroup analyses by ethnicity and gender were performed. Publication biases were assessed by funnel plots.
Table 1: Characteristics of included studies.

| Author/year | Nation    | Ethnicity | Diagnosis | Gender | Design         | Diagnostic criteria | Sample size | Case | V | M | VV | VM | MM | V | M | VV | VM | MM | Control | V | M | VV | VM | MM | HWE (P value) |
|-------------|-----------|-----------|-----------|--------|----------------|---------------------|--------------|------|---|---|----|----|----|---|---|----|----|----|-----------|---|---|----|----|----|-------------|
| Altintoprak AE, 2012 | Turkey | Asian | AD | Both | Case-control | DSM-IV | 110/330 | 139 | 81 | 47 | 45 | 18 | 399 | 261 | 137 | 125 | 68 | <0.01 |
| Celorio D, 2016 | Spain | Caucasian | AA | Both | Cohort | Altisent | 648/864 | 609 | 697 | NA | NA | NA | 817 | 943 | NA | NA | NA | 0.63 |
| Choi TY, 2006 | Korea | Asian | AD | Male | Case-control | DSM-IV | 108/76 | 136 | 80 | 45 | 46 | 17 | 110 | 42 | 38 | 34 | 4 | 0.30 |
| Enoch MA, 2006 | USA | Caucasian | AD | Both | Case-control | DSM-III-R | 176/133 | 257 | 95 | 91 | 75 | 10 | 175 | 91 | 59 | 57 | 17 | 0.58 |
| Gao LB, 2011 | China | Asian | AD | NA | Case-control | DSM-IV | 107/214 | 162 | 52 | 61 | 40 | 6 | 308 | 120 | 106 | 96 | 12 | 0.10 |
| Hallikainen T, 2000 | Finland | Caucasian | AD | Male | Case-control | DSM-III-R | 185/3407 | 161 | 209 | 32 | 97 | 56 | 3466 | 3348 | 880 | 1706 | 821 | 0.92 |
| Ishiguro H, 1999 | Japan | Asian | AD | Both | Case-control | DSM-IV | 175/346 | 244 | 106 | 85 | 74 | 16 | 480 | 212 | 166 | 148 | 32 | 0.91 |
| Kweon YS, 2005 | Korea | Asian | AD | Male | Case-control | DSM-IV | 97/94 | 144 | 50 | 54 | 36 | 7 | 132 | 56 | 47 | 38 | 9 | 0.75 |
| Liu Y, 2005 | Japan | Asian | AA | Both | Cohort | NA | 268/70 | 354 | 182 | 115 | 124 | 29 | 104 | 36 | 40 | 24 | 6 | 0.39 |
| Malhotra S, 2016 | India | Asian | AD | Male | Case-control | DSM-IV | 210/200 | 214 | 206 | 51 | 112 | 47 | 237 | 163 | 64 | 109 | 27 | 0.07 |
| Nakamura A, 2001 | Japan | Asian | AD | Male | Case-control | DSM-III | 91/112 | 132 | 50 | 45 | 42 | 4 | 153 | 71 | 49 | 55 | 8 | 0.16 |
| Nikolac M, 2013 | Croatia | Caucasian | AD | Both | Case-control | DSM-IV | 477/1197 | 464 | 490 | 117 | 230 | 130 | 1195 | 1199 | 289 | 617 | 291 | 0.29 |
| Pombo S, 2017 | Portugal | Caucasian | AD | Both | Case-control | DSM-IV-TR | 127/105 | 142 | 112 | 48 | 46 | 33 | 127 | 83 | 39 | 49 | 17 | 0.81 |
| Samochowiec J, 2008 | Poland | Caucasian | AD | Both | Case-control | ICD-10 | 48/150 | 61 | 35 | 20 | 21 | 7 | 153 | 147 | 42 | 69 | 39 | 0.33 |
| Schellekens AF, 2012 | Netherlands | Caucasian | AD | Male | Case-control | DSM-IV | 110/99 | 97 | 123 | 26 | 45 | 39 | 97 | 101 | 22 | 53 | 24 | 0.48 |
| Sery O, 2006 | Czech | Caucasian | AD | Both | Case-control | DSM-IV | 399/400 | 413 | 385 | 107 | 199 | 93 | 389 | 411 | 93 | 203 | 104 | 0.75 |
| Soyka M, 2015 I | Germany | Caucasian | AD | Both | Case-control | DSM-IV | 255/296 | 241 | 269 | 57 | 127 | 71 | 283 | 309 | 67 | 149 | 80 | 0.88 |
| Soyka M, 2015 II | Poland | Caucasian | AD | Both | Case-control | DSM-IV | 181/296 | 182 | 180 | 48 | 86 | 47 | 283 | 309 | 67 | 149 | 80 | 0.88 |
| Voisey J, 2011 | Australia | Caucasian | AD | Both | Case-control | DSM-IV | 227/219 | 231 | 223 | NA | NA | NA | 194 | 244 | NA | NA | NA | 0.05 |
| Wang X, 2011 | China | Asian | AD | Both | Case-control | DSM-IV | 107/214 | 162 | 52 | 61 | 40 | 6 | 308 | 120 | 106 | 96 | 12 | 0.10 |
| Zhang X, 2013 | China | Mixed | AA | Both | Case-control | DSM-IV | 126/146 | 148 | 104 | 41 | 66 | 19 | 155 | 137 | 41 | 73 | 32 | 0.96 |

AD: alcohol dependence; AA: alcohol abuse; V: Val; M: Met; HWE: Hardy-Weinberg equilibrium; NA: not available.
3. Results

3.1. Literature Search. In total, we identified 705 records. Of them, 180 records were erased because of duplication. After title and abstract screening, 502 irrelevant items were deleted. Of the remaining 43 publications, 23 ineligible publications were excluded based on inclusion and exclusion criteria. Ultimately, 20 articles [5, 8–26] remained for data combination. The study flow diagram is presented in Figure 1.

3.2. Characteristics of Eligible Studies. The main characteristics of the included studies are listed in Table 1. A total of 20 studies [5, 8–26] were included in this meta-analysis, including 18 case-control studies [5, 8, 10–14, 16–26] and 2 cohort studies [9, 15]. The studies were published between 1999 and 2017. Eighteen studies [27–32] were published in English, one [33] was in Chinese, and one [10] was in Korean. The study by Soyka et al. [23] consisted of a German cohort and a Poland cohort. Three of the studies were on alcohol abuse, and the rest of the studies were about alcohol dependence.

All the studies were in HWE with the exception of the study by Altintoprak et al. [8]. It should be pointed out that the participants in Zhang et al.’s study [26] were from different ethnicities. According to the NOS, the included studies received five or more stars (Table 2).

3.3. Meta-Analysis and Subgroup Analysis. Overall, 20 studies with 21 independent cohorts were included in quantitative analysis. The merged data indicated no significant association between rs4680 polymorphism and AUD under five genetic models in the overall population: V vs. M, OR = 1.02, 95%
CI 0.93–1.12, \(P = 0.70\) (Figure 2); VV vs. MM, OR = 0.99, 95% CI 0.79–1.23, \(P = 0.92\); VM vs. MM, OR = 0.91, 95% CI 0.81–1.03, \(P = 0.15\); VV+VM vs. MM, OR = 0.95, 95% CI 0.80–1.13, \(P = 0.65\); VV vs. VM+MM, OR = 1.04, 95% CI 0.91–1.18, \(P = 0.57\).

Subgroup analysis by ethnicity did not find any significant association of rs4680 and AUD in both Asians and Caucasians under any genetic model. Furthermore, we stratified the participants by gender. For the males, a marginally significant association was observed under the heterozygous model (VM vs. MM, OR = 0.81, 95% CI 0.67–0.98, \(P = 0.03\)). However, no significant association was detected under other genetic models. Regarding the females, rs4680 did not appear to be associated with AUD under five genetic models. Besides, subgroup analysis based on diagnosis still did not support any association of rs4680 and AUD. The summarized outcomes are displayed in Table 3.

### 3.4. Sensitivity Analysis and Publication Bias

After excluding the studies which were out of HWE, the recalculated effect sizes had no significant change. Therefore, it was not removed from the meta-analysis. The leave-one-out method was used to investigate the effect of an individual study on the pooled ORs and 95% CI. The results did not alter significantly through omitting any single study, indicating the stability of the outcomes. Furthermore, funnel plots did not have substantial asymmetry (Figure 3), suggesting there was no significant evidence of publication bias.

### 4. Discussion

Numerous meta-analysis studies have reported the associations of gene polymorphisms and AUD. For instance, Zhang et al.’s study [34] published in 2019 indicated that rs6296 polymorphism in the 5-HT1B gene was not associated with alcoholism. Villalba et al.’s study [35] in 2015 displayed that SLC6A4 promoter polymorphism was not associated with the risk for AUD, while Munafò et al.’s study [36] demonstrated that there was a significant but small association of the DRD2 Taq1A polymorphism with alcoholism. To our knowledge, this is the first meta-analysis study on rs4680 polymorphism in the COMT gene and AUD. We performed overall analysis and subgroup analysis by gender, ethnicity, and diagnosis. Our results suggested that rs4680 polymorphism in the COMT gene was not significantly linked to AUD in the overall population. However, a weak association was observed in males; carriers of VM genotype appeared to have an increased risk to AUD.

SNP rs4680 is a famous functional variant in the COMT gene. More than 40% of the enzymatic activity is affected by rs4680 polymorphisms. Numerous psychobiological disorders and clinical symptoms were proved to be associated with COMT gene polymorphisms. Gervasini et al.’s study [37] suggested COMT gene polymorphisms may contribute to the psychopathological symptoms of bulimia nervosa patients. Another study identified that different COMT genotypes may result in different motor behaviors [38]. A
study in 2015 indicated that polymorphism in the COMT gene was associated with Parkinson’s disease in a Japanese population. Apart from psychiatric disorders, COMT gene polymorphisms were also relevant to cancer risk. The relationship between functional polymorphisms in COMT and the risk of breast cancer is investigated by numerous studies.

### Table 3: Association between rs4680 polymorphism and alcohol use disorder.

| Genetic model | OR     | Association 95% CI | P value | No. of cohorts | Effect model | I² (%) | P value |
|---------------|--------|--------------------|---------|----------------|--------------|--------|---------|
| Overall       |        |                    |         |                |              |        |         |
| V vs. M       | 1.02   | 0.93-1.12          | 0.70    | 21             | R            | 53     | <0.01   |
| VV vs. MM     | 0.99   | 0.79-1.23          | 0.92    | 19             | R            | 52     | <0.01   |
| VM vs. MM     | 0.91   | 0.81-1.03          | 0.15    | 19             | F            | 26     | 0.14    |
| VV+VM vs. MM  | 0.95   | 0.80-1.13          | 0.56    | 19             | R            | 44     | 0.02    |
| VV vs. VM+MM  | 1.04   | 0.91-1.18          | 0.57    | 19             | R            | 34     | 0.08    |
| Asian         |        |                    |         |                |              |        |         |
| V vs. M       | 0.97   | 0.82-1.16          | 0.75    | 9              | R            | 51     | 0.04    |
| VV vs. MM     | 0.85   | 0.65-1.11          | 0.23    | 9              | F            | 40     | 0.10    |
| VM vs. MM     | 0.87   | 0.67-1.14          | 0.33    | 9              | F            | 3      | 0.41    |
| VV+VM vs. MM  | 0.86   | 0.67-1.11          | 0.25    | 9              | F            | 27     | 0.20    |
| VV vs. VM+MM  | 0.99   | 0.85-1.16          | 0.90    | 9              | F            | 40     | 0.10    |
| Caucasian     |        |                    |         |                |              |        |         |
| V vs. M       | 1.03   | 0.92-1.16          | 0.61    | 11             | R            | 59     | <0.01   |
| VV vs. MM     | 1.02   | 0.76-1.36          | 0.90    | 9              | R            | 62     | <0.01   |
| VM vs. MM     | 0.91   | 0.74-1.12          | 0.37    | 9              | R            | 42     | 0.09    |
| VV+VM vs. MM  | 0.94   | 0.76-1.17          | 0.60    | 9              | R            | 55     | 0.02    |
| VV vs. VM+MM  | 1.04   | 0.91-1.19          | 0.54    | 9              | F            | 39     | 0.11    |
| Male          |        |                    |         |                |              |        |         |
| V vs. M       | 0.92   | 0.81-1.05          | 0.24    | 11             | R            | 45     | 0.05    |
| VV vs. MM     | 0.87   | 0.60-1.24          | 0.43    | 10             | R            | 57     | 0.01    |
| VM vs. MM     | 0.81   | 0.67-0.98          | 0.03    | 10             | F            | 30     | 0.17    |
| VV+VM vs. MM  | 0.84   | 0.64-1.10          | 0.21    | 10             | R            | 46     | 0.06    |
| VV vs. VM+MM  | 0.92   | 0.78-1.08          | 0.30    | 10             | F            | 30     | 0.17    |
| Female        |        |                    |         |                |              |        |         |
| V vs. M       | 0.98   | 0.78-1.23          | 0.84    | 5              | R            | 64     | 0.03    |
| VV vs. MM     | 0.84   | 0.47-1.48          | 0.54    | 4              | R            | 56     | 0.08    |
| VM vs. MM     | 0.85   | 0.66-1.09          | 0.21    | 4              | F            | 0      | 0.47    |
| VV+VM vs. MM  | 0.83   | 0.65-1.05          | 0.12    | 4              | F            | 32     | 0.22    |
| VV vs. VM+MM  | 0.91   | 0.72-1.13          | 0.39    | 4              | F            | 49     | 0.12    |
| Alcohol dependence | | | | | | | |
| V vs. M       | 1.03   | 0.92-1.14          | 0.63    | 18             | R            | 55     | <0.01   |
| VV vs. MM     | 0.98   | 0.78-1.23          | 0.85    | 17             | R            | 53     | <0.01   |
| VM vs. MM     | 0.90   | 0.79-1.01          | 0.08    | 17             | F            | 27     | 0.14    |
| VV+VM vs. MM  | 0.93   | 0.78-1.11          | 0.43    | 17             | R            | 45     | 0.02    |
| VV vs. VM+MM  | 1.06   | 0.93-1.20          | 0.39    | 17             | F            | 26     | 0.39    |
| Alcohol abuse |        |                    |         |                |              |        |         |
| V vs. M       | 0.98   | 0.75-1.28          | 0.87    | 3              | R            | 61     | 0.07    |
| VV vs. MM     | 1.05   | 0.38-2.91          | 0.92    | 2              | R            | 66     | 0.09    |
| VM vs. MM     | 1.37   | 0.80-2.35          | 0.26    | 2              | F            | 0      | 0.56    |
| VV+VM vs. MM  | 1.25   | 0.76-2.07          | 0.38    | 2              | F            | 37     | 0.21    |
| VV vs. VM+MM  | 0.84   | 0.39-1.80          | 0.65    | 2              | R            | 77     | 0.04    |

OR: odds ratio; CI: confidence interval; F: fixed-effects model; R: random-effects model.
all over the world. However, the results were inconsistent and contradictory. An updated meta-analysis on this issue published in 2012 suggested that rs4680 polymorphism is not associated in breast cancer susceptibility [39]. Another meta-analysis study in 2020 showed that there was no association between rs4680 polymorphism and endometrial cancer risk [40].

In the present work, we included 20 articles worldwide, of which 3 studies were from China. Most of these studies showed that there was no statistically significant association between COMT gene polymorphisms and AUD risk. After combining the results of all included studies, the pooled meta-analysis results remained the same. We also conducted the subgroup analysis divided by ethnicity and gender; all the results were turned out to be negative. Therefore, we could only come to a conclusion that there was no association between COMT gene polymorphisms and alcohol dependence risk.

COMT was first reported in 1958 [41]. COMT has multiple SNPs; rs4680 polymorphism is among them. rs4680 polymorphism could significantly affect protein abundance and enzyme activity, but it could not alter the mRNA expression levels. The different enzyme activity between alleles may be attributed to differences in protein integrity. Chen et al.'s study [6] demonstrated that the influence of rs4680 SNP on COMT activity is independent from three other SNPs in the COMT gene.

COMT mainly prevails as an S isoform in the cytoplasm. It is widely distributed in most tissues including the liver and pituitary gland, cerebellum, lungs, mammary glands, etc. [42, 43]. Guanine-to-adenine transition at codon 158 accounts for valine (Val) to methionine (Met) substitution, thus leading to the alteration of COMT enzyme activity. Val/Val, Val/Met, and Met/Met genotypes represent high, medium, and low activity, respectively, since the COMT enzyme is essential to dopamine degradation. It is possible that this functional polymorphism may contribute to the underlying molecular mechanisms of AD.

Some drawbacks of the present work should not be neglected. First, although we have gathered the most comprehensive original studies on this issue worldwide, the study number and the sample size are relatively small and thus may lead to a possibility of false negative. Second, it is clear that COMT polymorphisms have significant impact on the enzyme activity. However, we did not found any association between rs4680 polymorphism and AUD susceptibility in the overall population; the underlying mechanisms are yet an unanswered question. Third, the occurrence of AUD is thought to be determined by the combined effects of the intrinsic factor and environment factor; we only concentrated on the genetic influences. Fourth, the $P$ value for the HWE test of one included study is <0.05, which means that the included participants of this study may not be representative. Last but not the least, we only searched the online databases in English and Chinese; relevant articles written in other languages were not included in this work, which may lead to selection bias.

5. Conclusion

The present study suggests that rs4680 polymorphism has no association with AUD in the overall population, but it has a weak association with AUD in males. Carriers of VM genotype in males appear to have an increased risk to AUD. Considering the limitations of this study, future well-designed studies with large sample sizes are encouraged.

Data Availability

All analyses of this work were based on previously published literatures and public databases.

Conflicts of Interest

All authors involved in this work declared that there was no conflict of interests.
Authors’ Contributions

Xin-Rong Jin created this idea and produced the first version of this draft. Xin-Rong Jin and Zhi-Qiang Zhao finished the literature searching and data extraction, respectively. Xin-Rong Jin critically examined the final manuscript and checked out all the data analyses.

References

[1] A. Batra, C. A. Müller, K. Mann, and A. Heinz, “Alcohol dependence and harmful use of alcohol: Diagnosis and Treatment Options,” Deutsches Ärzteblatt International, vol. 113, no. 17, pp. 301–310, 2016.

[2] J. Rehm, C. Mathers, S. Popova, M. Thavorncharoenasap, Y. Teerawattananon, and J. Patra, “Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders,” Lancet, vol. 373, no. 9682, pp. 2223–2233, 2009.

[3] D. M. Dick and T. Foroud, “Genetic strategies to detect genes involved in alcoholism and alcohol-related traits,” Alcohol Research & Health, vol. 26, no. 3, pp. 172–180, 2002.

[4] B. Verhulst, M. C. Neale, and K. S. Kendler, “The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies,” Psychological Medicine, vol. 45, no. 5, pp. 1061–1072, 2015.

[5] H. Ishiguro, T. H. Shibuya, M. Toru, T. Saito, and T. Arinami, “Association study between high and low activity polymorphism of catechol-O-methyltransferase gene and alcoholism,” Psychiatric Genetics, vol. 9, no. 3, pp. 135–138, 1999.

[6] J. Chen, B. K. Lipska, N. Halim et al., “Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain,” The American Journal of Human Genetics, vol. 75, no. 5, pp. 807–821, 2004.

[7] K. Ryckman and S. M. Williams, “Calculation and use of the Hardy-Weinberg model in association studies,” Current Protocols in Human Genetics, vol. 57, no. 1, 2008.

[8] A. E. Alintoprak, B. Kayahan, B. Tezcanli, B. Kosova, and H. Coşkunol, “Catechol-O-methyltransferase Val108/158Met gene and alcoholism in Turkish subjects,” Turkish Journal of Medical Sciences, vol. 42, no. 2, pp. 289–297, 2012.

[9] D. Celorrio, X. Muñoz, P. Amiano et al., “Influence of dopaminergic system genetic variation and lifestyle factors on excess alcohol consumption,” Alcohol and Alcoholism, vol. 51, no. 3, pp. 258–267, 2016.

[10] T. Y. Choi, H. N. Kim, D. H. Han, K. J. Min, Y. S. Lee, and C. Na, “Relationship between alcohol withdrawal symptoms and dopaminergic gene polymorphisms (DRD2, DAT, COMT) in alcohol dependence patients,” Korean Journal of Biological Psychiatry, vol. 13, no. 3, pp. 178–188, 2006.

[11] M. A. Enoch, J. F. Waheed, C. R. Harris, B. Albaugh, and D. Goldman, “Sex differences in the influence of COMT Val158Met on alcoholism and smoking in plains American Indians,” Alcoholism, Clinical and Experimental Research, vol. 30, no. 3, pp. 399–406, 2006.

[12] L. B. Gao, S. R. Zhong, X. J. Wang et al., “Association between alcohol dependence syndrome and COMT genetic polymorphism in Yunnan Han nationality,” Advances in Modern Biomedicine, vol. 11, no. 15, pp. 2822–2827, 2011.

[13] T. Hallikainen, H. Lachman, T. Saito et al., “Lack of association between the functional variant of the catechol-O-methyltransferase (COMT) gene and early-onset alcoholism associated with severe antisocial behavior,” American Journal of Medical Genetics, vol. 96, no. 3, pp. 348–352, 2000.

[14] Y. S. Kweon, H. K. Lee, C. T. Lee, and C. U. Pae, “Association study of catechol-O-methyltransferase gene polymorphism in Korean male alcoholics,” Psychiatric Genetics, vol. 15, no. 2, pp. 151–154, 2005.

[15] Y. Liu, K. Yoshimura, T. Hanaoka et al., “Association of habitual smoking and drinking with single nucleotide polymorphism (SNP) in 40 candidate genes: data from random population-based Japanese samples,” Journal of Human Genetics, vol. 50, no. 2, pp. 68–69, 2005.

[16] S. Malhotra, D. Basu, M. Khullar, A. Ghosh, and N. Chugh, “Candidate genes for alcohol dependence: a genetic association study from India,” The Indian Journal of Medical Research, vol. 144, no. 5, pp. 689–696, 2016.

[17] A. Nakamura, T. Inada, Y. Kitao, and Y. Katayama, “Association between catechol-O-methyltransferase (COMT) polymorphism and severe alcoholic withdrawal symptoms in male Japanese alcoholics,” Addiction Biology, vol. 6, no. 3, pp. 233–238, 2001.

[18] M. Nikolac, M. Sagud, G. Nedic et al., “The lack of association between catechol-O-methyl-transferase Val108/158Met polymorphism and smoking in schizophrenia and alcohol dependence,” Psychiatry Research, vol. 205, no. 1-2, pp. 179-180, 2013.

[19] S. Pombo, J. Ferreira, P. Q. Levy, and M. Bicho, “Is there a genetic support for the Cloninger (type I/II) clinical classification of alcohol addiction?,” Psychiatry Research, vol. 258, pp. 621–623, 2017.

[20] J. Samochowiec, J. Kucharska-Mazur, A. Grzywacz et al., “Genetics of Lesch’s typology of alcoholism,” Progress in Neuro-Psychopharmacology & Biological Psychiatry, vol. 52, no. 2, pp. 423–427, 2008.

[21] A. J. Schellekens, B. Franke, B. Ellenbroek et al., “Reduced dopamine receptor sensitivity as an intermediate phenotype in alcohol dependence and the role of the COMT Val158Met and DRD2 Taq1A genotypes,” Archives of General Psychiatry, vol. 69, no. 4, pp. 339–348, 2012.

[22] O. Serý, W. Didden, V. Mikes, R. Petlová, V. Znojil, and P. Zvolský, “The association between high-activity COMT allele and alcoholism,” Neuro Endocrinology Letters, vol. 27, no. 1-2, pp. 231–235, 2006.

[23] M. Soyka, P. Zill, G. Koller, A. Samochowiec, A. Grzywacz, and U. W. Preuss, “Val158Met COMT polymorphism and risk of aggression in alcohol dependence,” Addiction Biology, vol. 20, no. 1, pp. 197–204, 2015.

[24] J. Voisey, C. D. Swagell, I. P. Hughes, B. R. Lawford, R. M. D. Young, and C. Morris, “A novel SNP in COMT is associated with alcohol dependence but not opiate or nicotine dependence: a case control study,” Behavioral and Brain Functions, vol. 7, no. 1, p. 51, 2011.

[25] X. Wang, S. Zhong, L. Gao et al., “An association study between polymorphism of alcohol dehydrogenase (ADH1B), aldehyde dehydrogenase (ALDH2), cytochrome (CYP4502E1), catechol-O-methyltransferase (COMT) and 5-hydroxytryptamine transporter (5-HTT) genes in Yunnan Han population with alcohol dependence,” African Journal of Biotechnology, vol. 10, no. 57, pp. 12164–12170, 2011.

[26] X. Zhang, M. R. Lee, B. J. Salmeron et al., “Prefrontal white matter impairment in substance users depends upon the
catechol-o-methyl transferase (COMT) val158met polymorphism,” *NeuroImage*, vol. 69, pp. 62–69, 2013.

[27] D. Nagaya, Z. Zahari, M. Saleem, B. H. Yahaya, S. C. Tan, and N. M. Yusoff, “An analysis of genetic association in opioid dependence susceptibility,” *Journal of Clinical Pharmacy and Therapeutics*, vol. 43, no. 1, pp. 80–86, 2018.

[28] M. Hashemi, M. Shakiba, S. Sanaei et al., “Evaluation of prodynorphin gene polymorphisms and their association with heroin addiction in a sample of the southeast Iranian population,” *Molecular Biology Research Communications*, vol. 7, no. 1, pp. 1–6, 2018.

[29] T. K. Clarke, L. Ambrose-Lanci, T. N. Ferraro et al., “Genetic association analyses of PDYN polymorphisms with heroin and cocaine addiction,” *Genes, Brain, and Behavior*, vol. 11, no. 4, pp. 415–423, 2012.

[30] S. G. Wei, Y. S. Zhu, J. H. Lai, H. X. Xue, Z. Q. Chai, and S. B. Li, “Association between heroin dependence and prodynorphin gene polymorphisms,” *Brain Research Bulletin*, vol. 85, no. 3–4, pp. 238–242, 2011.

[31] T. K. Clarke, K. Krause, T. Li, and G. Schumann, “An association of prodynorphin polymorphisms and opioid dependence in females in a Chinese population,” *Addiction Biology*, vol. 14, no. 3, pp. 366–370, 2009.

[32] J. Yuanyuan, S. Rui, T. hua et al., “Genetic association analyses and meta-analysis of dynorphin-kappa opioid system potential functional variants with heroin dependence,” *Neuroscience Letters*, vol. 685, pp. 75–82, 2018.

[33] J. Wei, S. JianGuo, A. Lei, and Z. Rui, “Association between polymorphism in 3′ untranslated regions of prodynorphin gene and heroin dependence,” *Progress in Modern Biomedicine*, vol. 10, no. 13, pp. 2439–2441, 2010.

[34] X. Zhang, X. Geng, N. Sun et al., “There is no association between rs6296 and alcoholism: a meta-analysis,” *Journal of Ethnicity in Substance Abuse*, pp. 1–13, 2019.

[35] K. Villalba, J. Attonito, A. Mendy, J. G. Devieux, J. Gasana, and T. M. Dorak, “A meta-analysis of the associations between the SLC6A4 promoter polymorphism (5HTTLPR) and the risk for alcohol dependence,” *Psychiatric Genetics*, vol. 25, no. 2, pp. 47–58, 2015.

[36] M. R. Munafò, I. J. Matheson, and J. Flint, “Association of the DRD2 gene Taq1A polymorphism and alcoholism: a meta-analysis of case-control studies and evidence of publication bias,” *Molecular Psychiatry*, vol. 12, no. 5, pp. 454–461, 2007.

[37] G. Gervasini, L. M. Gonzalez, S. Mota-Zamorano et al., “Association of COMT Val158Met polymorphism with psychopathological symptoms in patients with eating disorders,” *Current Molecular Medicine*, vol. 18, no. 1, pp. 65–70, 2018.

[38] N. Nogueira, M. F. B. Bacelar, B. P. Ferreira, J. O. Parma, and G. M. Lage, “Association between the catechol-O-methyltransferase (COMT) Val158Met polymorphism and motor behavior in healthy adults: a study review,” *Brain Research Bulletin*, vol. 144, pp. 223–232, 2019.

[39] X. Qin, Q. Peng, A. Qin et al., “Association of COMT Val158Met polymorphism and breast cancer risk: an updated meta-analysis,” *Diagnostic Pathology*, vol. 7, no. 1, p. 136, 2012.

[40] P. Kumar, G. Singh, and V. Rai, “Evaluation of COMT gene rs4680 polymorphism as a risk factor for endometrial cancer,” *Indian Journal of Clinical Biochemistry*, vol. 35, no. 1, pp. 63–71, 2020.