Academia Open
Vol 10 No 2 (2025): December (in progress)
DOI: 10.21070/acopen.10.2025.1171 . Article type: (Science)

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ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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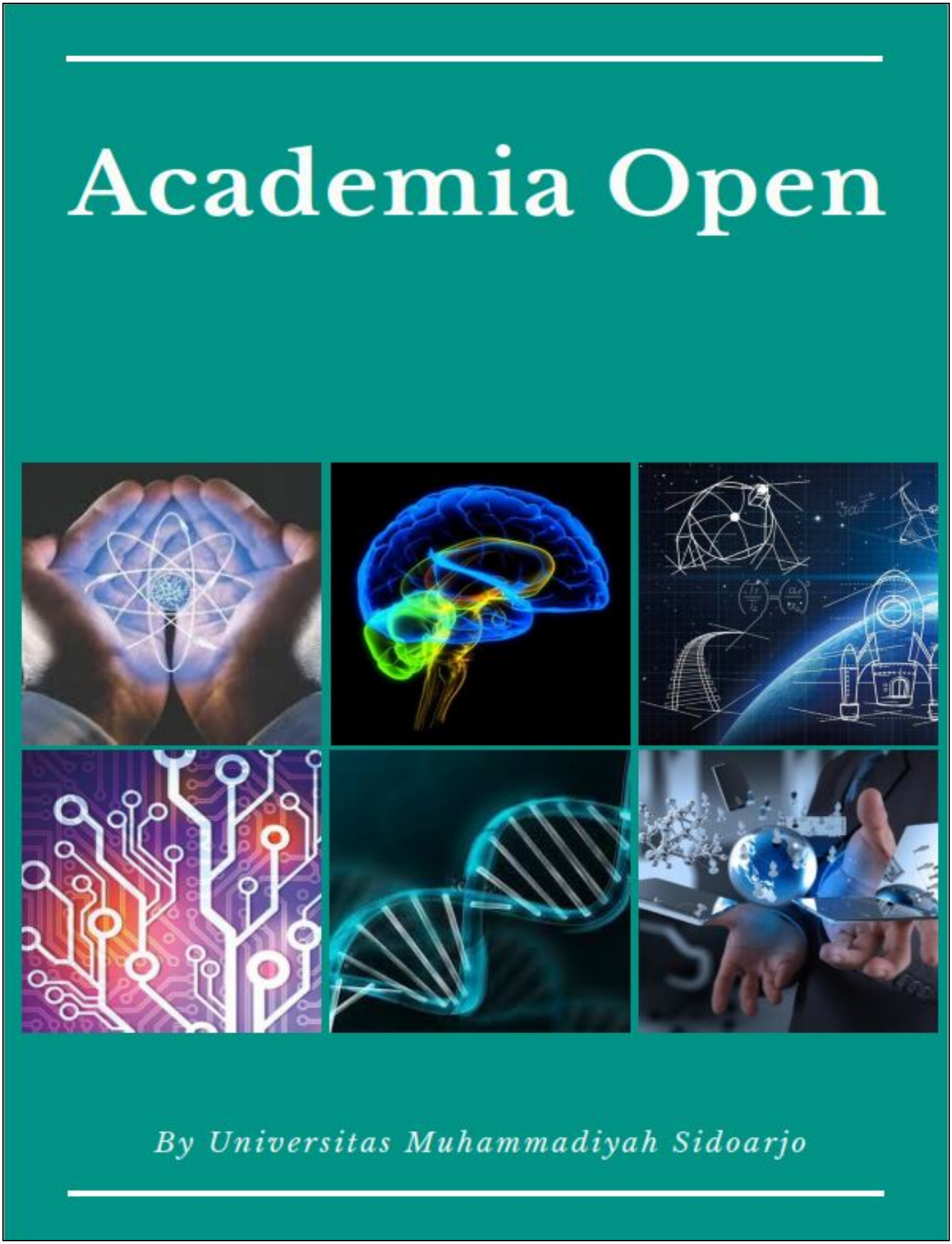

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ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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Relationships between addiction and the COMT rs4680 Gene Polymorphism

Hubungan antara kecanduan dan Polimorfisme Gen COMT rs4680

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Abstract

General Background: Addiction to drugs and alcohol is a complex neuropsychiatric disorder influenced by both environmental and genetic factors, particularly those affecting dopamine regulation. **Specific Background:** The catechol-O-methyltransferase (COMT) gene, particularly the rs4680 Val158Met polymorphism, plays a crucial role in dopamine metabolism and has been implicated in addiction susceptibility. **Knowledge Gap:** While several studies link COMT variants to substance use disorders, evidence from Middle Eastern populations, especially Iraq, remains limited. **Aims:** This study aimed to assess the association between the COMT rs4680 polymorphism and vulnerability to drug and alcohol addiction in an Iraqi male cohort. **Results:** Analysis of 90 samples revealed a significantly higher frequency of the A allele and AA genotype in addicts compared to controls. The AA genotype was associated with a 14.55-fold and 17.14-fold increased risk of drug and alcohol addiction, respectively, while the GA genotype showed intermediate risk. **Novelty:** This is among the first studies to examine this genetic association in an Iraqi context, highlighting the contribution of COMT polymorphism to addiction predisposition. **Implications:** The findings suggest potential for genetic screening and personalized intervention strategies targeting dopaminergic pathways in addiction prevention and treatment.

Highlight :

- The A allele of the rs4680 polymorphism is significantly associated with increased addiction risk.
- The AA genotype shows a strong correlation with both drug and alcohol addiction.
- The GA genotype indicates moderate vulnerability to addictive behavior.

Keywords : rs4680 Polymorphism, COMT Gene, Addiction, Drug Use, Alcohol Use

Published date: 2025-07-20 00:00:00

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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Introduction

Addiction to drugs and alcohol are severe, multifaceted neuropsychiatric conditions that can cause death as well as social, economic, and health issues for both the addict and society. A complex interplay of genetic, psychological, and environmental variables leads to these issues. Because substance use disorders are multifaceted, the American Psychiatric Association has categorized them as mental disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[1,2]. Additionally, it refers to a person's inability to function normally without a narcotic chemical in his body. Addiction is a periodic or chronic poisoned state that is detrimental to both the individual and society, according to the World Health Organization. Recurrent usage of a synthetic or natural substance causes this syndrome [3]. Additionally, it entails a complex interplay between environmental and genetic factors that manifests as behavioral changes in people who are frequently exposed to an addictive substance [4] . The Catechol-O-Methyltransferase (COMT) gene is one of the genetic variables that has received a lot of attention lately. It is essential for controlling the levels and metabolism of catecholamine neurotransmitters, such as dopamine, which is a neurotransmitter that is crucial for the brain's reward system, particularly in the prefrontal cortex, which is linked to impulse control and decision-making. It can be found in postsynaptic neurons and glial cells [5,6,7].

Catechol-O-Methyltransferase (COMT) gene and Polymorphism

In region 11.2 (22q11.2) on the long arm of the 22nd chromosome the gene is located. There are six exons in the gene. The third exon is where the enzyme's translation starts, while the first and second exons are non-coding [8,9] . Two copies of short mRNA that code for a protein in the soluble form S-COMT, which contains 50 amino acids and is present in most tissues, are produced by the gene's two promoters, which regulate the transcription of distinct mRNAs. It is shorter than the lengthy mRNA copy and accounts for a minor portion of the COMT enzyme's overall activity [6 , 10] . The membrane-bound protein COMT (MB-COMT), which is produced by the lengthy mRNA transcript, is essential for the biological action and metabolism of dopamine because it catalyzes the biotransformation of catecholamine neurotransmitters, including dopamine[10 , 11] . Single nucleotide polymorphisms (SNPs) in this human gene, such as SNP rs4633 in the coding region 3, rs737865 in the first non-coding region, and rs165599 in the 3′ untranslated region, may impact gene expression and consequently the activity or efficacy of the enzyme [12, 13]. Furthermore, by strengthening the control of COMT gene transcription, rs737865 and rs2020917 in the first promoter area (Promoter 1) impact MB-COMT activity [14,15]. The most prevalent and extensively researched genetic variant in coding region 4, rs4680 val 158 met, is responsible for the substitution of the nitrogenous base G in the codon (GTG) encoding the amino acid valine with the nitrogenous base A in the codon (ATG). This results in the amino acid methionine at codon 108 in the soluble protein S-COMT and codon 158 in the membrane-associated protein MB-COMT [6,16,17]. This causes an enzyme to be 40% less active, less structurally stable, and more thermally volatile. These two amino acids have three to four times different enzymatic activity, but they may also express more of the enzyme than the normal one [6,18]. This leads to a slower breakdown of dopamine at the synapse and a higher concentration of dopamine in the prefrontal cortex (Saloner et al., 2020). The homozygous methionine variant, on the other hand, leads in lower synaptic dopamine levels, a more stable and effective enzyme for the metabolism of norepinephrine and dopamine in the prefrontal cortex and reward systems, and a higher degree of enzyme activity. According to Saloner et al. (2020)[19] and Lovallo et al. (2020) [20], the heterozygous val/met variation exhibits intermediate enzyme activity. [16]. According to a study on drug addiction, those who use more than two drugs are more likely to have the Val/Val genotype than those who have the heterozygous Val/Met genotype. Additionally, genetic diversity may influence substance use susceptibility and addictive traits, according to the study's findings [16]. Additionally linked to the intensity and modifications of alcohol cravings during abstinence was the homozygous met/met mutation [21]. Tolcapone is used in a trial of COMT inhibition to treat alcohol use disorder in people with impaired cortical dopamine transmission. Following genotyping of the rs4680 gene variant, the study discovered that tolcapone decreased the effect of COMT, which in turn decreased alcohol cravings, and that the val allele significantly affects COMT activity. Thus, the study came to the conclusion that COMT inhibition might lower alcohol intake, particularly in people who are genetically prone to high COMT activity and potentially low cortical dopamine levels [22]. Compared to the Val allele, the Met allele of the COMT Val158Met polymorphism boosts dopamine (DA) bioavailability in the prefrontal cortex and slows metabolism. It follows that on executive function tests, healthy Met carriers do better than Val carriers. But according to a study, this benefit vanishes when methamphetamine (METH) use develops [19].

Thus, the purpose of the current investigation was to determine whether drug and alcohol addiction and the COMT gene's rs4680 genetic polymorphism are related.

Methods

Two distinct sites—Al-Atta Hospital for Addiction Treatment and Psychological Rehabilitation and Al-Qana Center for Social Rehabilitation—were used to gather human samples. Three equal sets of 90 samples were used: 30 samples were from drug users, 30 samples were from alcohol users, and 30 samples were from the control group. Based on the categories that were available during the study period, the sample comprised a range of age groups from 12 to 70 years. All participants gave their informed consent, and the sample and data collecting procedures were conducted in strict accordance with the ethical standards authorized by the Iraqi Ministry of Health. To

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preserve the samples and guarantee DNA stability, blood was extracted using 3-milliliter tubes that included EDTA as an anticoagulant. The tubes were then taken to the Wahj Al-Dana Rehabilitation, Training, and Services Company laboratory to finish the analytical processes. The Zymo Research Quick-gDNATM Blood MiniPrep kit was used to extract DNA, and agarose gel electrophoresis was used to analyze the results in accordance with Sambrook et al.'s 1989 methodology.

Thermo Fisher Scientific Company's TaqMan custom SNP genotyping test is then used to identify SNP COMT rs4680 val158met. SNP information are displayed in table (1). Also, real-time PCR (real-time polymerase chain reaction) was used to apply the allele-specific discriminating technique.

Context Sequence [VIC/FAM]	Assay ID	SNP ID
CCAGCGGATGGTGGATTTCGCTGGC[A/G]TGAAGGACAAGGTGTGCATGCCTGA	C-25746809_50	COMT rs4680Val158Met

Table 1. *Details of SNPs.*

Statistical Analysis

The direct counting method was used to determine the genotype and allele frequencies for SNPs. Each SNP's Hardy-Weinberg equilibrium (HWE) was examined using Michael H. Court's online calculator (2005–2008). The population is consistent with HWE if the p-value is greater than 0.05. In contrast, the odds ratio (OR), which is determined by chi-square and Fisher's exact probability using the statistical program epidemiology (WINPEPI) version 11.65, was evaluated in order to assess the risk associated with genotypes. Additionally, p-values below 0.05 are considered statistically significant.

Results and Discussion

The current study's findings suggest a possible genetic link between the risk of drug addiction and the rs4680 polymorphism in the COMT gene. The prevalence of the mutant A allele among addicts was much higher (45%) than in the control group (18.3%) , indicating that the two groups' Hardy-Weinberg equilibrium has been broken. Carriers of the A allele are around four times more likely than non-carriers to acquire addiction, according to Fisher's exact test, which showed a strong correlation between the A allele and the risk of addiction with a high likelihood ratio (P = 0.002) and an OR value of 3.64. Upon genotyping analysis, it was found that the heterozygous genotype (GA) doubled the risk of addiction; nevertheless, this association fell short of statistical significance (P = 0.173) , this could result from the sample size or the interplay of additional environmental and genetic factors. On the other hand, the homozygous genotype (AA) clearly had an impact, as it was linked to a 14.55-fold increased risk of addiction, with a statistically significant effect (P = 0.017), demonstrating the impact of the dosage of the mutant allele on raising the susceptibility to addiction , as shown in Table (2).

allele frequency	Drug addictNo.= 30(100%)	ControlNo.= 30(100%)	OR (95 % CI)	p-value
G	33(55)	49(81.7)		
A	27(45)	11(18.3)	3.64(1.60- 8.29)	0.002**
Genotype frequency				
GG	11(37)	20(67)		
GA	11(37)	9(30)	2.2(0.72- 6.84)	0.173
AA	8(26)	1(3)	14.55(1.69 - 125.01)	0.017 *

Table 2. *Numbers and percentage frequencies of COMT genotypes, alleles, and their Hardy-Weinberg equilibrium (HWE) in drug addict compared with control groups*

Significantly* (p≤0.05); highly Significantly** (p≤0.01); non- significant: NS, OR: Odds ratio; 95% CI: 95% confidence interval; p: Two-tailed Fisher exact probability; Hardy-Weinberg equilibrium (HWE).

As demonstrated in Table (3), the frequency distribution of the G and A alleles of the rs4680 genetic form and the analysis of the genetic equilibrium law using the Hardy-Weinberg equilibrium law revealed a discernible difference in the genetic distribution between the alcoholic group and the control group, suggesting a potential connection between the genetic form and the onset of addiction. Alcoholics had a 48.3% frequency of the mutant A allele compared to an 18.3% frequency in the control group. In the same two groups, the normal G allele was present at 51.7% and 81.7%, respectively. A significant four-fold (OR 4.17) connection between the A allele and the risk of alcohol addiction was found using the Fisher's test, with a 95% confidence interval (CI) (1.84 - 9.46) . In contrast to the control group at a P = 0.001 level of probability The findings indicated that the homozygous mutant genotype

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(AA) for the rs4680 gene form had a ten-fold higher risk of addiction (OR=17.14(1.86-158.22), whereas carriers of the heterozygous genotype (GA) had a five-fold increased risk (OR=5.40(1.70-17.17). This relationship was statistically significant at the probability level of P = 0.015.

allele frequency	Alcohol addict No.= 30(100%)	ControlNo.= 30(100%)	OR (95 % CI)	p-value
G	31(51.7)	49(81.7)		
A	29(48.3)	11(18.3)	4.17(1.84 - 9.46)	0.001**
Genotype frequency				
GG	7(23.3)	20(67)		
GA	17(56.7)	9(30)	5.40(1.70-17.17)	0.005**
AA	6(20)	1(3)	17.14(1.86 - 158.22)	0.015 *

Table 3. *Numbers and percentage frequencies of COMT genotypes, alleles, and their Hardy-Weinberg equilibrium (HWE) in alcohol addict compared with control groups.*

Significantly* (p≤0.05); highly Significantly** (p≤0.01); non- significant: NS , OR: Odds ratio; 95% CI: 95% confidence interval; p: Two-tailed Fisher exact probability; Hardy-Weinberg equilibrium (HWE).

According to [24], addictive disorders, including alcohol and drug abuse, are complicated worldwide health issues that result from the interplay of genetic, psychological, and environmental factors. The dopamine system in the brain is one of the biochemical and genetic factors that different forms of addiction share, according to recent research. The COMT (catechol-O-methyltransferase) gene, which breaks down neurotransmitters like dopamine in the brain's frontal cortex, is one of the genes that has drawn more attention in this context [1]. This enzyme, which is found in higher brain regions like the prefrontal cortex, is an essential target in addiction research and psychiatry because it helps maintain the balance of dopamine activity and compensates for dopamine transporter deficiency [25]. A person's susceptibility to impulsiveness and addictive behavior, whether related to alcohol or drugs, is increased by the genetic polymorphism G/A Val158Met, which alters the enzyme's activity and impacts dopamine levels [26]. This was demonstrated by the current study's results, which showed a substantial correlation between the drugs (OR=3.64 and OR=14.55) and alcohol (OR=4.17 and OR=17.4) addiction risk and the A allele, represented by Met, and its homozygous genotype, AA, represented by Met/Met. Although the risk of alcohol addiction was significantly higher for the mixed genotype GA Val/Met by up to five times (OR=5.40) than for drug addiction (OR=2.2), this difference was not significant when compared to the control group. This relates to the genetic form of addicts because, contrary to those who have the homozygous Met 158 AA, who exhibit low enzyme activity and high dopamine levels, carriers of the homozygous Val 158 GG are likely to have high enzyme activity and low dopamine levels [27]. It is also possible to differentiate the Met158 version of COMT, which produces an enzyme with 40% less activity and is more thermally volatile and structurally less stable. Three to four times as much enzyme activity separates these two categories of amino acids [6 , 18], This causes dopamine concentration in the prefrontal cortex to rise and dopamine breakdown at the synapse to slow down [19]. In contrast, the normal val/val allele of the gene results in a more stable and effective enzyme that metabolizes norepinephrine and dopamine in the reward systems and prefrontal cortex. Its enzyme activity is more than 40% higher than that of the homozygous methionine allele, and its synaptic dopamine levels are lower. According to [19 , 20], and [16], the heterozygous val/met variation exhibits intermediate enzyme activity. The study [10] found that people with the Met allele have higher levels of emotionality and anxiety, which makes them more prone to utilize stimulants or alcohol as a coping mechanism. Our findings support this finding. They are also more prone to engage in impulsive behaviors and seek out potent stimulants because to their higher reward sensitivity and greater brain reaction to emotional stimuli. These factors enhance the likelihood of addiction, particularly to alcohol and stimulants [28]. In people with one or two copies of the COMT 158Met allele, Lovallo et al. (2020) showed that early childhood adversity exposure impairs stress responses, which in turn contributes to potentially dangerous alcohol and drug use behaviors. Additionally, Zhao et al. (2020)[29] showed a possible correlation between the COMT rs4680 single nucleotide polymorphism (SNP) and the vulnerability to dyskinesia in Chinese individuals as well as interindividual variation in daily levodopa dose. The Met/Met genotype of heroin users has a longer duration of addiction than other genetic variants, according to [16] , who also discovered that genetic variation may influence addictive features and vulnerability to drug use. According to [21] , COMT polymorphisms might be indirectly related to the intensity and fluctuation of alcohol cravings while abstinent. Volkow et al. (2010)[30] shown that addicts' sensitivity to natural reinforcers decreases as a result of their dopamine function declining. In addition to improving frontal lobe function and improving inhibitory control, therapeutic therapies that target the brain's dopamine response and cortical area activity can also decrease impulsivity and compulsive drug usage while encouraging the addict to participate in non-drug-related activities. According to [31], alcohol addiction and schizophrenia are linked to the rs4680 genetic variant in combination with another rs165774 genetic variant. Additionally, [32] found that those who are homozygous for the Met/Met genotype are more likely to experience structural alterations in white matter, which could be a factor in the prefrontal cortex's structural and functional deficiencies that have been linked to addiction in the past. Although Damardeh and Alireza, 2019; Cao et al., 2003 found no correlation between COMT rs4680 polymorphisms and opioid addiction, the current study's findings were in conflict with Wang et al., 2011, who reported significant differences in the frequency of COMT gene polymorphisms, including rs4680, between alcoholics and controls.

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Conclusion

The study found a strong correlation between a higher risk of drug and alcohol addiction and the A allele of the COMT rs4680 polymorphism. The GA genotype had a moderate correlation with the degree of addiction risk, but those with the AA genotype were more prone to addiction. This implies that the A allele gradually influences addictive behavior.

References

1. F. Dahmardeh dan A. Rezaeifar, "Effect of rs4680 (Val158Met) Polymorphism of the COMT Gene on Opioid Addiction in an Iranian Population: A Case-Control Study," Gene Cell Tissue, vol. 6, no. 2, pp. e91912, Apr. 2019, doi: 10.5812/gct.91912.
2. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Publishing, 2022.
3. A. N. Ahmed, "The Role of Social Awareness in Protecting University Students from Drugs in the Current Stage: Iraq as a Model," Center for Educational and Psychological Research, University of Baghdad, pp. 1–29, 2018.
4. J. Chmielowiec et al., "Associations Between the Dopamine D4 Receptor and DAT1 Dopamine Transporter Genes Polymorphisms and Personality Traits in Addicted Patients," Int. J. Environ. Res. Public Health, vol. 15, no. 10, 2018, doi: 10.3390/ijerph15102076.
5. D. Mier, P. Kirsch, dan A. Meyer-Lindenberg, "Neural Substrates of Pleiotropic Action of Genetic Variation in COMT: A Meta-Analysis," Mol. Psychiatry, 2009, doi: 10.1038/mp.2009.36.
6. A. E. Tammimäki dan P. T. Männistö, "Are Genetic Variants of COMT Associated with Addiction?" Pharmacogenet. Genomics, vol. 20, pp. 717–741, 2010, doi: 10.1097/FPC.0b013e328340bdf2.
7. E. M. Tunbridge et al., "The Role of Catechol-O-Methyltransferase in Reward Processing and Addiction," CNS Neurol. Disord. Drug Targets, vol. 11, pp. 306–323, 2012, doi: 10.2174/187152712800672409.
8. J. Tenhunen et al., "Genomic Organization of the Human Catechol-O-Methyltransferase Gene and Its Expression From Two Distinct Promoters," Eur. J. Biochem., vol. 223, pp. 1049–1059, 1994.
9. E. M. Tunbridge, T. A. Lane, dan P. J. Harrison, "Expression of Multiple Catechol-O-Methyltransferase (COMT) mRNA Variants in Human Brain," Am. J. Med. Genet. B, vol. 144B, pp. 834–839, 2007.
10. K. Chmielowiec et al., "Associations Between the COMT rs4680 Gene Polymorphism and Personality Dimensions and Anxiety in Patients With a Diagnosis of Other Stimulants Dependence," Genes, vol. 13, no. 10, p. 1768, 2022, doi: 10.3390/genes13101768.
11. D. N. Salman, Relationship Between COMT and MAOA Genes Polymorphisms With Aggressive Behavior in Convicted People, MSc Thesis, University of Basrah, 2022.
12. N. J. Bray et al., "A Haplotype Implicated in Schizophrenia Susceptibility Is Associated With Reduced COMT Expression in Human Brain," Am. J. Hum. Genet., vol. 73, pp. 152–161, 2003, doi: 10.1086/376578.
13. E. L. Dempster et al., "The Quantification of COMT mRNA in Post Mortem Cerebellum Tissue: Diagnosis, Genotype, Methylation and Expression," BMC Med. Genet., vol. 7, p. 10, 2006, doi: 10.1186/1471-2350-7-10.
14. Y. Ji et al., "Breast Cancer Risk Reduction and Membrane-Bound Catechol-O-Methyltransferase Genetic Polymorphisms," Cancer Res., vol. 68, no. 14, pp. 5997–6005, 2008, doi: 10.1158/0008-5472.CAN-08-0043.
15. H. Xia, N. Wu, dan Y. Su, "Investigating the Genetic Basis of Theory of Mind (ToM): The Role of Catechol-O-Methyltransferase (COMT) Gene Polymorphisms," PLoS One, vol. 7, no. 11, p. e49768, 2012, doi: 10.1371/journal.pone.0049768.
16. J. A. Sonia et al., "Catechol-O-Methyltransferase and Dopamine Receptor D4 Gene Variants: Possible Association With Substance Abuse in Bangladeshi Male," PLoS One, vol. 16, no. 2, p. e0246462, 2021, doi: 10.1371/journal.pone.0246462.
17. D. N. Salman dan A. I. Al-Badran, "Relationship Between COMT and MAOA Genes Polymorphisms and Aggressive Behavior," J. Biotechnol. Biol., vol. 1, pp. 1–14, 2023, doi: 10.17303/jbb.2023.1.105.
18. X. Wang 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," Afr. J. Biotechnol., vol. 10, no. 57, pp. 12164–12170, 2011, doi: 10.5897/AJB11.959.
19. R. Saloner et al., "COMT val158met Genotype Alters the Effects of Methamphetamine Dependence on Dopamine and Dopamine-Related Executive Function: Preliminary Findings," Psychiatry Res., vol. 292, p. 113269, 2020, doi: 10.1016/j.psychres.2020.113269.
20. W. R. Lovallo et al., "Early Life Adversity and Blunted Stress Reactivity as Predictors of Alcohol and Drug Use in Persons With COMT (rs4680) Val158Met Genotypes," Alcohol Clin. Exp. Res., vol. 43, no. 7, pp. 1519–1527, 2020, doi: 10.1111/acer.14079.
21. D. Czarnecki et al., "Initial Study on COMT and DRD2 Gene Polymorphisms as Well as the Influence of Temperament and Character Trait on the Severity of Alcohol Craving in Alcohol-Dependent Patients," J. Clin. Med., vol. 10, no. 5892, 2021, doi: 10.3390/jcm10245892.
22. J. P. Schacht et al., "Effects of Pharmacological and Genetic Regulation of COMT Activity in Alcohol Use Disorder: A Randomized, Placebo-Controlled Trial of Tolcapone," Neuropsychopharmacology, vol. 47, pp. 1953–1960, 2022, doi: 10.1038/s41386-022-01335-z.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

23. J. Sambrook, E. Fritsch, dan T. Maniatis, Molecular Cloning: A Laboratory Manual, 2nd ed. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 1989.
24. A. S. Hatoum et al., "Multivariate Genome-Wide Association Meta-Analysis of Over 1 Million Subjects Identifies Loci Underlying Multiple Substance Use Disorders," Nat. Ment. Health, vol. 1, pp. 210–223, 2023, doi: 10.1038/s44220-023-00034-y.
25. R. L. Yu et al., "Interactions of COMT and ALDH2 Genetic Polymorphisms on Symptoms of Parkinson's Disease," Brain Sci., vol. 11, no. 3, p. 361, 2021, doi: 10.3390/brainsci11030361.
26. Y. Paloyelis et al., "DAT1 and COMT Effects on Delay Discounting and Trait Impulsivity in Male Adolescents With Attention Deficit/Hyperactivity Disorder and Healthy Controls," Neuropsychopharmacology, vol. 35, pp. 2414–2426, 2010, doi: 10.1038/npp.2010.124.
27. E. M. Tunbridge, P. J. Harrison, dan D. R. Weinberger, "Catechol-O-Methyltransferase, Cognition, and Psychosis: Val158Met and Beyond," Biol. Psychiatry, vol. 60, pp. 141–151, 2006, doi: 10.1016/j.biopsych.2005.10.024.
28. D. Barman et al., "A Meta-Analysis for Understanding the Role of the COMT Val158Met Variant in the Susceptibility to Alcoholism," Afr. J. Alcohol Drug Abuse, vol. 11, 2024, doi: 10.4314/ajada.v11i1.2.
29. C. Zhao et al., "Genetic Variations in Catechol-O-Methyltransferase Gene Are Associated With Levodopa Response Variability in Chinese Patients With Parkinson's Disease," Sci. Rep., vol. 10, p. 9521, 2020, doi: 10.1038/s41598-020-65332-2.
30. N. D. Volkow et al., "Imaging Dopamine's Role in Drug Abuse and Addiction," Neuropharmacology, vol. 56, no. Suppl. 1, pp. 3–8, 2010, doi: 10.1016/j.neuropharm.2008.05.022.
31. J. Voisey et al., "A Novel SNP in COMT Is Associated With Alcohol Dependence but Not Opiate or Nicotine Dependence: A Case Control Study," Behav. Brain Funct., vol. 7, p. 51, 2011, doi: 10.1186/1744-9081-7-51.
32. X. Zhang 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, Apr. 2013, doi: 10.1016/j.neuroimage.2012.11.056.

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