

NQO1 and NQO2 Gene Polymorphisms Related to Methamphetamine-Associated Psychosis in the Makassar Population, Indonesia

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ABSTRACT

Introduction: This study investigates the relationship between NQO1 and NQO2 gene polymorphisms and methamphetamine-associated psychosis (MAP) in the Makassar population.

Methods: Case-Control Study to determine the role of the NQO1 and NQO2 genes in the onset of psychotic symptoms due to methamphetamine abuse. The control group consists of individuals who consume methamphetamine without psychotic characteristics (n=139), while the case group consists of individuals who consume methamphetamine with psychotic characteristics (n=128).

Results: The NQO1 gene polymorphism demonstrates a significant association with the duration of MAP, with the TT genotype and the

T allele occurs more frequently in prolonged cases. The CT genotype is linked to an increased risk of spontaneous relapse, while the TT genotype is more prevalent among patients with polysubstance abuse. Additionally, the NQO2 (I/D) gene polymorphism indicates a trend towards differential genotype distribution in patients with MAP, with the DD genotype appearing more frequently in prolonged cases, and the I allele associated with a heightened risk of spontaneous relapse.

Conclusion: These findings suggest that polymorphisms in the NQO1 and NQO2 genes may play a role in the susceptibility to and clinical manifestations of MAP within the Makassar population.

Keywords: Methamphetamine, NQO1, NQO2 gene, psychosis

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INTRODUCTION

The international abuse of methamphetamine, a stimulant substance formerly known for causing addiction primarily in Japan, has now become a severe public health threat with global repercussions. Although substance abuse is derived from the complex interplay of social, environmental, and psychological factors, evidence has shown that genetics play a contributing role in increasing susceptibility to these types of addictions (1). This perspective on genetic predisposition allows for a clear path to better and more granular in the biological pathways that are driving methamphetamine dependency, and mining risk assessment, prevention, and targeted interventions in at-risk populations worldwide (2).

The development of psychotic symptoms in methamphetamine users is associated with specific genetic variations, particularly in dopamine-related genes and glutamate receptor genes (3,4). Research indicates that single nucleotide polymorphisms (SNPs) and methylation patterns in genes such as DRD4 and COMT play significant roles in the manifestation of these symptoms (5,6).

Emerging studies indicate that oxidative stress is significantly involved in the neurotoxic effects of methamphetamine, particularly through its impact on dopamine pathways. Following exposure to methamphetamine, dopamine is displaced from its vesicular storage to the cytoplasm, where it undergoes auto-oxidation, yielding

Highlights

- NQO variants relate to MAP duration with significant association.
- TT genotype and T allele of NQO1 occur more in prolonged MAP.
- CT genotype of NQO1 increases risk of relapse in patients with MAP.
- NQO2 I/D polymorphism shows distinct genotype patterns in MAP.
- I allele of NQO2 may increase spontaneous relapse risk in MAP.

dopamine-quinones and various reactive oxygen species (7). These toxic by-products may play a critical role in the neurodegenerative processes associated with methamphetamine-associated psychosis (MAP) and other cognitive impairments related to MAP. Understanding this oxidative mechanism not only enhances our knowledge of methamphetamine's neurotoxic actions but also suggests potential therapeutic targets to mitigate the significant neurological and psychiatric effects of methamphetamine abuse (8).

In particular, genetic polymorphisms in the NQO genes have shown significant associations with various diseases including susceptibility and other chronic conditions, especially in the case of NQO2. NQO2 gene promoter region insertion/deletion (I/D) polymorphism had been associated in cases of idiopathic Parkinson's disease (9). Increased dopaminergic activity above baseline during cued food stimulation has also been associated with schizophrenia (10). Importantly, such associations have not been observed for the NQO1 gene, or other polymorphic loci in the NQO2 gene. This specificity suggests that the NQO2 gene may play a distinct role in vulnerability to oxidative stress-related conditions, potentially due to its influence on reactive oxygen species production and cellular detoxification pathways (11).

In light of the established role of oxidative stress in the neurochemical changes caused by methamphetamine use, the association between NQO gene polymorphisms and methamphetamine abuse is of great interest. Methamphetamine administration can induce the release of DOP and DOP is known to undergo auto-oxidation generating highly reactive dopamine-quinone and reactive oxygen species, which points to oxidative stress being involved in methamphetamine neurotoxicity. Thus, exploring the genetic variations occurring in NQO1 and NQO2 among methamphetamine users may indicate a genetic susceptibility to oxidative impairment (12).

Abuse of methamphetamine is significantly associated with the risk of psychosis in humans; in some cases, individuals subsequently present with chronic psychotic symptoms that may persist beyond acute intoxication. The neurotoxicity of methamphetamine, especially via the oxidative stress routes has been well documented. However, the genetic determinants of MAP are poorly understood. A number of earlier studies indicated that polymorphisms of oxidative stress-related genes comprised NQO1 and NQO2, can modulate methamphetamine user's susceptibility to psychosis. This study aims to fill this gap by investigating the association between NQO1 and NQO2 polymorphisms and MAP in the Makassar population.

METHODS

The methodology of this research has been meticulously designed to adhere to the highest ethical and scientific standards, commencing with the approval from the Drug Abuse Ethics Committee of the Faculty of Nursing, Makassar Health Polytechnic. Each participant provided written consent, underscoring their commitment to ethical conduct in genetic research, particularly given the sensitive nature of the DNA analyses involved. This study employs a case-control design to investigate the genetic predisposition associated with MAP, focusing on participants diagnosed in accordance with the Diagnostic Criteria for Research (DCR) of the International Classification of Diseases (ICD-10) for F15.2 (dependence syndrome) and F15.5 (psychotic disorder). This approach ensures the selection of clinically relevant samples, thereby enhancing the specificity of the genetic findings.

The sample population comprises 128 patients diagnosed with MAP, including both outpatient and inpatient cases at the Psychiatric Hospital in Makassar, Indonesia. These cases were meticulously matched with 139 control subjects exhibiting comparable demographics in terms of age, gender, and geographical background, which enhances the internal validity of the study. The control group consisted of residents of Makassar, predominantly medical professionals, selected to minimise confounding factors related to substance dependence and mental disorders, as they had no personal or family history of these conditions. The comprehensive selection criteria for both groups facilitated a robust comparative analysis, thereby enhancing the reliability of the findings and their relevance in understanding genetic factors in MAP within the target population.

To obtain a comprehensive understanding of MAP, a targeted methodology was developed that categorises patients into specific clinical subgroups. There are three clusters of clinical subgroups: individuals with psychosis caused by confirmed methamphetamine use (MAP), patients with or without a history of spontaneous relapse, and individuals with or without a history of concurrent polysubstance abuse. To enhance specificity, the MAP group was further categorised based on the duration of psychosis. Those who experience persistent MAP, characterised by symptoms lasting more than one month, are compared to patients who experience transient MAP, where symptoms improve within one month. This refined categorisation framework facilitates a focused examination of the differential impact of methamphetamine on the duration of MAP and the tendency for relapse, thereby revealing significant genetic and clinical differences. By isolating these variables, this study aims to enhance our understanding of the neuropsychiatric implications of MAP, which informs targeted intervention strategies for different patient subpopulations.

For the I/D polymorphism in the NQO2 promoter region, PCR amplification was conducted using primers 5'-CTGCCTGGAAGTCAGCAGGGTC-3' and 5'-CTCTTTACGCAGCGCCTAC-3' at a heating temperature of 64°C. This resulted in distinct product differences: 291 bp for the I/I genotype, 262 bp for the D/D genotype, and a unique heteroduplex of 310 bp alongside fragments of 291 bp and 262 bp for the I/D genotype (11). This methodological approach ensures high specificity in genotype classification, thereby facilitating a detailed examination of genetic variants associated with MAP susceptibility.

Statistical Analysis

Statistical analysis was conducted using SPSS (version 26, Inc., Chicago, IL, USA). A crosstab test was performed, including the chi-square test and Pearson correlation, along with assumption tests for normality and linearity. Both data sets (cases and controls) were evaluated for normality, with results indicating a normal distribution, followed by a linearity test. The outcomes of this test determined whether the data from the two groups (controls and cases) exhibited differences and whether there was a relationship between them in the context of NQO1 and NQO2 polymorphisms. A significance level was established at a p-value threshold of 0.05, enabling us to draw meaningful conclusions regarding the genetic relationship with MAP susceptibility. Differences in genotype distribution between patients and controls were analysed using the corrected continuity test and Odds Ratio (OR) based on two-sided p-values.

Ethical approval

Ethical approval for this study was obtained from the Health Research Ethics Committee of Makassar Health Polytechnic or Komite Etik Penelitian Kesehatan (KEPK) Politeknik Kesehatan Makassar (Approval Number: 1070/M/KEPK-PTKMS/VII/2024) on July 2, 2024. This study complies with the Declaration of Helsinki and has obtained informed consent from all participants while maintaining confidentiality and voluntary consent.

RESULTS

Sociodemographic Characteristics of Patients with MAP in the Makassar Population

The patient population has an average age of approximately 34.39 years, with a standard deviation of 11.86 years, indicating a wide age range. The age group distribution reveals that the majority of cases occur within the 20-39 years age range, with 28.1% in the 20-29 age group and 28.5% in the 30-39 age group. This pattern suggests that young to middle-aged adults are more likely to experience psychosis as a result of methamphetamine use, potentially due to higher exposure to methamphetamine within this age group. The significant p-value (p

= 0.000) further highlights the meaningful differences in distribution among age groups (Table 1).

Gender data indicates that the prevalence of MAP is marginally higher among women (55.4%) than men (44.6%). These findings may reflect distinct gender patterns in substance use or socio-cultural factors that influence drug use behaviour within the Makassar population. A p-value of 0.000 suggests a significant association between gender and MAP in this population (Table 1).

Education and employment data indicate that a significant proportion of patients possess a basic education level (43.4%), followed by those with a medium education level (40.1%), while a smaller percentage have attained a higher education level (16.5%). Employment status reveals that a slightly higher number of patients are engaged in jobs related to their field (51.3%), compared to those who are not working (48.7%). This trend may suggest a correlation between lower educational attainment, types of employment, and increased vulnerability to substance-related mental health issues, potentially as a result of socioeconomic stress (Table 1).

The predominance of younger individuals with lower education levels may indicate that socioeconomic challenges and a lack of awareness about drug risks contribute significantly to the onset of psychosis. Additionally, the slightly higher female representation could suggest sociocultural factors unique to the Makassar population, potentially related to stress, stigma, or access to healthcare and rehabilitation services. Meanwhile, the almost equal employment distribution implies that psychosis does not significantly discriminate by employment status but may reflect stressors or drug access associated with occupational environments. (Figure 1).

Genotype and Allele Frequencies of MAP in the Patient Population of Makassar

The research results indicate the frequency of genotypes and alleles for the NQO1 gene, ranging from 0.544 to 0.767. The study found that

Table 1. Sociodemographic characteristics of patients with methamphetamine-induced psychosis in the Makassar population

Characteristics	Total, n (%)	p value
Age, mean ± SD (years)	34.39 ± 11.86	
<20	30 (11.2)	0.000
20 – 29	75 (28.1)	
30 – 39	76 (28.5)	
40 – 49	62 (23.2)	
>50	24 (9.0)	
Sex		0.000
Male	119 (44.6)	
Female	148 (55.4)	
Education level		0.000
Basic Education	116 (43.4)	
Moderate Education	107 (40.1)	
High Education	44 (16.5)	
Employment		0.000
Employed	137 (51.3)	
Unemployed	130 (48.7)	

MAP was present in a significant proportion of patients, with an average prevalence of 0.835 compared to a range of 0.510 to 1.367. The frequency of MAP was also substantial, with an average of 0.049 for both positive and negative cases. Additionally, the frequency of spontaneous relapse was significant, with an average of 0.273 for positive cases and 0.639 for negative cases. Furthermore, the study identified a notable number of patients with a history of substance abuse (Table 2).

The data reveals statistically significant differences in genotype and allele distributions across various conditions, highlighting the influence of age and education. In MAP, both transient and prolonged cases demonstrate notable p-values (e.g., p=0.003 and p=0.007), suggesting an association between specific genotypes and psychosis. For spontaneous relapse, the distribution of C and T alleles significantly varies, with a lower odds ratio (OR=0.273) in the “positive” group, indicating a potential protective effect

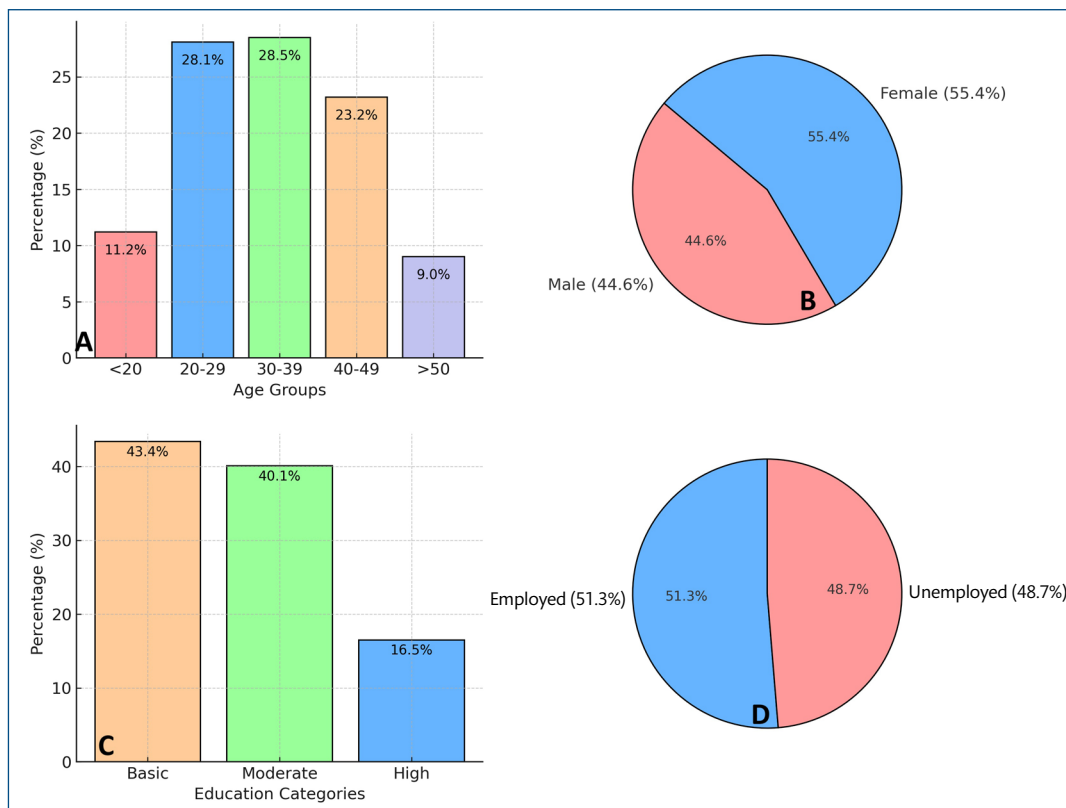


Figure 1. The updated visualizations now include captions for better interpretability: A) presents the age distribution of patients, describing the spread across age groups; B) highlights the gender ratio of patients, showcasing the proportion of males and females; C) displays the education levels of patients, illustrating the distribution among various education categories; and Figure 4 depicts the employment status of patients, emphasizing the division between employed and unemployed groups.

against relapse. Additionally, in polysubstance abuse, the TT genotype shows a strong association with higher prevalence ($p=0.001$), and the OR values further suggest an increased likelihood of polysubstance abuse among TT carriers (Figure 2).

The data indicate that there is no significant difference in genotype and allele frequencies between the patient and control groups. However, the results vary in other patient cohorts. In the MAP group, the frequencies of the CC and CT genotypes differed significantly, whereas no significant difference was observed in the allele frequencies. The spontaneous relapse group exhibited a significant difference in the frequency of the T allele, while the genotype frequencies did not show significant variation. In the polydrug abuse group, both genotype and allele frequencies were significantly different.

Genotype and Allele Frequency in Patients with MAP and Control Subjects

The frequency of genotypes and alleles of the insertion-deletion (I/D)

polymorphism in the promoter region of the NQO2 gene and its association with mental health conditions and behaviours are presented in Table 3. Genotype frequencies are categorised as II, ID, and DD, while allele frequencies are indicated as I and D (Figure 1). The study findings reveal that the incidence of MAP is significantly higher in patients diagnosed with MAP compared to the control group. Furthermore, the rate of spontaneous relapses is also elevated among patients with MAP. Additionally, the prevalence of polydrug abuse is greater in this patient population. The research results suggest that the occurrence of MAP is influenced by multiple factors, including the type of substance abuse and the frequency of polydrug use.

The data suggests that the examined SNPs do not significantly influence susceptibility to MAP in this population. The near-identical allele and genotype distributions between case and control groups support this conclusion. While small sample sizes may limit the study’s power, the consistent lack of divergence indicates these SNPs are not major determinants of MAP risk (Figure 3).

Table 2. Genotype and allele frequencies for the polymorphism NQO1 gene

	n	Genotype (%)			p value	Allele (%)		P value (OR, 95% CI)
		CC	CT	TT		C	T	
Case	128	47 (36.7)	65 (50.8)	16 (12.5)	0.554	172 (67.2)	84 (32.8)	0.835 (0.510-1.367)
Control	139	57 (41)	64 (46)	18 (12.9)		197 (70.9)	81 (29.1)	
MAP	99	37 (37.4)	50 (50.5)	12 (12.1)	0.003	137 (69.2)	61 (30.8)	1.240 (1.098-1.401)
Transient	78	36 (46.1)	35 (44.9)	7 (9)	0.003	80 (74.1)	28 (25.9)	1.292 (1.068-1.562)
Prolonged	40	11 (27.5)	24 (60)	5 (12.5)	0.007	50 (62.5)	30 (37.5)	0.688 (0.494-0.957)
Spontaneous relapse								
Positive	40	16 (40)	18 (45)	6 (15)	0.000	55 (37.4)	92 (62.6)	0.273 (0.138-0.540)
Negative	70	22 (31.4)	39 (55.7)	9 (12.9)	0.049	25 (34.2)	48 (65.8)	0.639 (0.530-0.772)
Polysubstance abuse								
Yes	76	27 (35.5)	35 (46.1)	14 (18.4)	0.001	98 (64.5)	54 (35.5)	0.565 (0.454-0.702)
No	34	10 (29.4)	20 (58.8)	4 (11.8)	0.048	47 (69.1)	21 (30.9)	0.750 (0.627-0.897)

MAP: Methamphetamine associated psychosis.

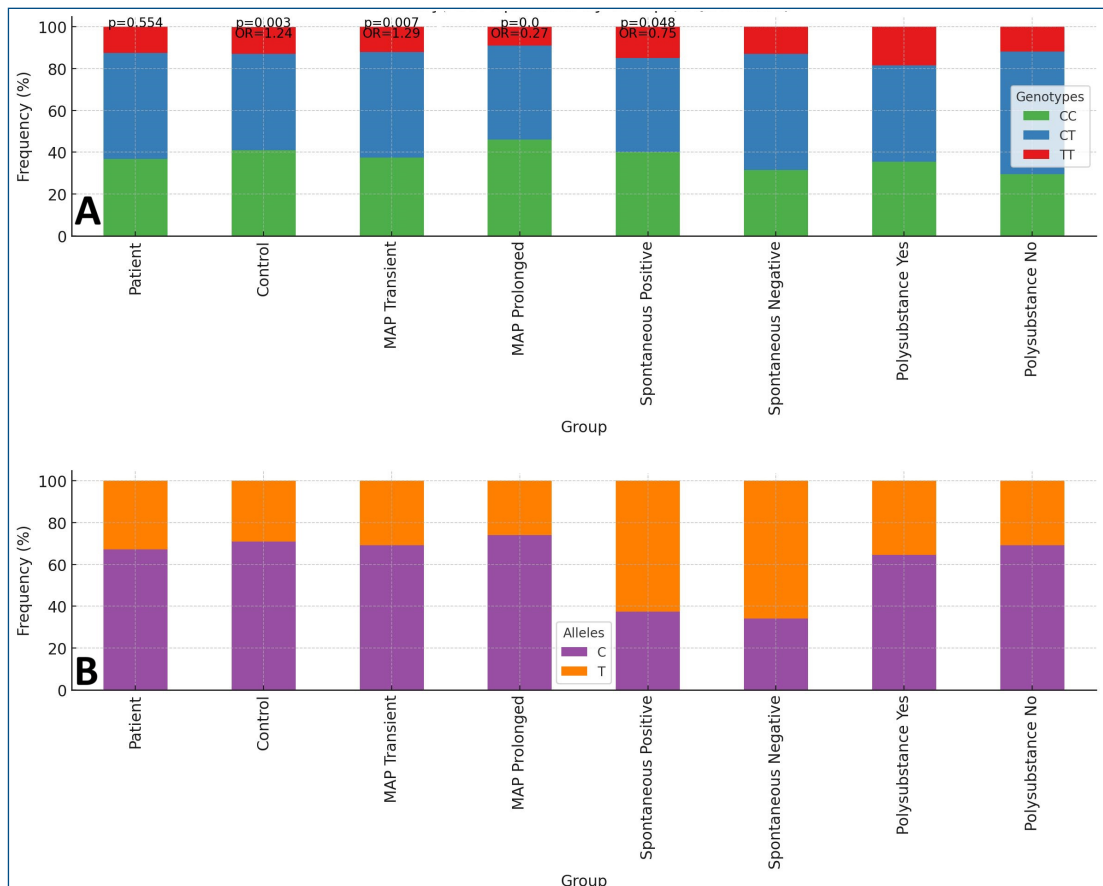


Figure 2. Genotype and Allele Frequencies of the NQO1 Gene Across Different Groups. A) Illustrates the distribution of genotypes (CC, CT, TT). B) Shows allele frequencies (C, T). Statistical values, including p-values and odds ratios (OR), are annotated for each group. These values highlight significant differences and associations observed in the study. The use of contrasting colors enhances the clarity and appeal of the visualization.

Table 3. Genotype and allele frequencies for the insertion I deletion (I / D) polymorphism in the promoter region of the NQO2 gene

	n	Genotype (%)			p value	Allele (%)		P value (OR, 95% CI)
		II	ID	DD		I	D	
Case	128	78 (60.9)	40 (31.3)	10 (7.8)	0.937	230 (81.6)	52 (18.4)	1.053 (0.644-1.720)
Control	139	83 (59.7)	50 (36)	6 (4.3)		252 (81.6)	57 (18.4)	
MAP	99	62 (62.6)	27 (27.3)	10 (10.1)	0.000	178 (89.9)	20 (10.1)	0.139 (0.078-0.247)
Transient	54	32 (59.3)	18 (33.3)	4 (7.4)	0.000	96 (88.8)	12 (11.2)	5.500 (2.267-13.345)
Prolonged	40	26 (65)	9 (22.5)	5 (12.5)	0.000	73 (91.2)	7 (8.8)	2.800 (1.387-5.654)
Spontaneous relapse								
Positif	40	25 (62.5)	12 (30)	3 (7.5)	0.000	75 (93.8)	5 (6.2)	5.00 (1.817-13.757)
Negative	70	42 (60)	21 (30)	7 (10.0)	0.000	124 (88.6)	16 (11.4)	0.143 (0.072-0.284)
Polysubstance abuse								
Yes	76	45 (59.2)	24 (31.6)	7 (9.2)	0.000	135 (88.8)	17 (11.2)	0.143 (0.072-284)
No	34	23 (67.6)	9 (26.5)	2 (5.9)	0.012	64 (94.1)	4 (5.9)	0.470 (0.112-3.107)

MAP: Methamphetamine associated psychosis.

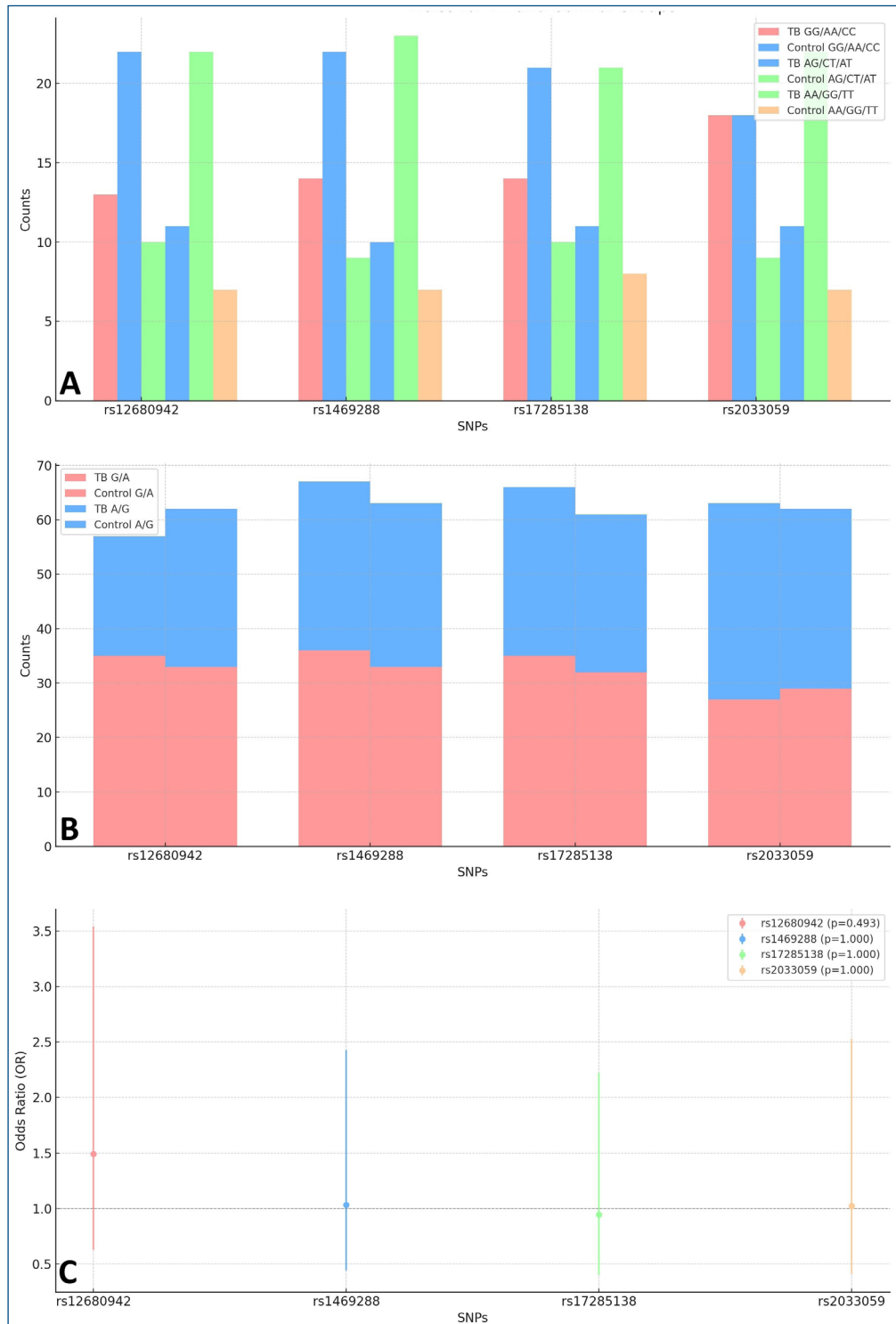


Figure 3. The updated visualizations now include captions for better interpretability, providing a comprehensive comparative analysis of genotypes and alleles in case and control groups for four SNPs (rs12680942, rs1469288, rs17285138, rs2033059). A) Compares genotype frequencies (GG/AA/CC, AG/CT/AT, AA/GG/TT) between the groups. B) Presents allele distributions (G vs. A, T vs. C) as stacked bar charts. C) Highlights odds ratios (OR) with 95% confidence intervals (CI) for each SNP, emphasizing statistical insignificance with p-values greater than 0.05.

DISCUSSION

This study aimed to identify genetic susceptibility factors for methamphetamine-associated psychosis (MAP) in the Makassar population, focusing on polymorphisms in the NQO1 and the NQO2 genes.

The data indicates a significant prevalence of methamphetamine-induced psychosis among individuals aged 20–39, which corresponds with the early patterns of substance use commonly observed in young adults. The relatively young average age (34.39 ± 11.86 years) with substantial variation highlights the necessity of exploring age-specific genetic, environmental, and neurobiological factors that may affect vulnerability. These demographic insights can direct biomolecular studies on age-related gene expression and neuroadaptive responses elicited by methamphetamine, thereby informing early intervention strategies aimed at young adults.

For the purpose of this study, spontaneous relapse is defined as a replenishment of methamphetamine use occurring during the study period, without requiring an external intervention. Patients carrying the CT genotype of the NQO1 gene have a highly significantly higher risk for spontaneous relapse. This is in accordance with previous studies showing that genetic factors might predict whether a substance-dependent individual relapses or not. Methamphetamine use is common among young adults, with some studies reporting high rates of methamphetamine use and MAP. Past-year methamphetamine use among adults aged 18–34 is estimated to be 1.02% in the U.S. (13), while lifetime prevalence in Iran is 7.1% (14). Psychotic manifestations are also prevalent in methamphetamine users, where 70.9% have experienced psychosis (15), and a half (55.7%) had relapse (16).

Biological features play an important role in both methamphetamine addiction and the risk of MAP. Methamphetamine exposure induces brain region molecular signatures including reward and motivation-related areas as well as gene signatures specific to microglial cells in the orbitofrontal cortex (17). Developmental susceptibility is heterogeneous, as in utero exposure leads to long term behavioral deficits (18). Genetic predisposition is also factor, for example, the BDNF Val66Met polymorphism, which increases the risk in Met/Met female mice (19). Single-cell RNA sequencing has helped uncover methamphetamine induced neuroinflammatory and epigenetic modifications (20,21). Investigating these pathways may inform new therapeutic approaches, including neuroprotective and anti-inflammatory interventions (22,23).

The distribution of genotypes (CC, CT, TT) and allele frequencies (C, T) is presented for both patients and controls. There was no significant difference in the genotype distribution between the observed patients and controls, with the p-value indicating no association. Similarly, the allele frequencies (alleles C and T) also showed no significant differences, with an odds ratio (OR) close to 1, suggesting that the allele distribution is relatively balanced between the groups.

When comparing transient and prolonged MAP, the CC genotype appears to be more prevalent in transient cases, while the TT genotype is more frequently observed in prolonged cases. The distribution of allele frequencies also indicates a higher prevalence of the T allele in prolonged cases. Statistically, this comparison yields a significant p-value, supporting the possibility of a relationship between NQO1 gene polymorphism and the persistence of MAP.

Furthermore, substance abuse is more prevalent in certain genotypes (CT and TT), with a significant p-value indicating a relationship between the polymorphism and susceptibility to substance abuse. These findings suggest an association between the NQO1 gene polymorphism and

psychiatric conditions, including MAP, spontaneous relapse, and a propensity for substance abuse. The significant p-values and odds ratios observed in several comparisons reinforce the role of this gene as a genetic marker for susceptibility to specific psychiatric responses and behaviours.

The study conducted by Mcketin et al. (2017) compared transient MAP, persistent MAP, and primary psychosis, highlighting differences in the types of delusions and hallucinations experienced. Persistent MAP is associated with more complex symptoms compared to transient MAP (24). A related study by Hung et al. (2005) indicated that individuals with the MTHFR 677 TT genotype present with lower serum and red blood cell folate concentrations and elevated plasma homocysteine levels when compared to those with the CC genotype. However, this is observed in the context of folate metabolism, rather than psychosis (25). These findings confirm the existence of various types of psychosis and several genetic associations, thereby indirectly supporting the assertion regarding the prevalence of CC and TT genotypes in cases of transient versus prolonged MAP.

For the purpose of this study, spontaneous relapse is defined as a replenishment of methamphetamine use occurring during the study period, without requiring an external intervention. Patients carrying the CT genotype of the NQO1 gene have a highly significantly higher risk for spontaneous relapse. This is in accordance with previous studies showing that genetic factors might predict whether a substance-dependent individual relapses or not. The commonality between spontaneous relapse and polysubstance abuse indicates a potential genetic predisposition that deserves further investigation into

Aside from environmental context, genes influencing spontaneous relapse and polysubstance abuse, especially NQO2 and dopamine receptor (DRD2) genes, also contribute. Alleles II have been reported to present a higher risk for relapse while allele I may share a higher susceptibility (26). Genotype II was primarily observed in polysubstance users while genotype DD was somewhat more prevalent in non-users. The genetic basis of substance use disorders is complex, and it emphasises how certain genes related to ACE and dopamine receptors can predispose an individual to addiction (27).

Relapse is a notorious hurdle on the road to recovery from addiction, and engaging in polydrug use has been found to heighten the risk of doing so (28). Risk factors are benzodiazepine use, several attempts to detoxify and frequent visits to emergency unit. On the other hand, high relapse rates have been associated with certain genetic polymorphisms, such as MTHFR C677>T (29) and IL28B rs12979860 (30), although no association was found in a study on methamphetamine dependence (28). Associations of the CT genotype of the MDR-1 C3435T with poor treatment outcomes, reinforcing the genetic basis of relapse vulnerability. Understanding these genetic influences may help in tailoring more effective addiction interventions.

We observed that the Genotype (II, ID, DD) and allele frequencies (I, D) exhibited minimal differences between patients with MAP and the control group, with the p-value indicating no overall significant relationship. In both patients and controls, allele I is dominant, demonstrating no strong correlation with disease susceptibility when evaluated solely based on this polymorphism.

Our findings contradict previous studies that did not identify a significant relationship between genotype polymorphisms (II, ID, DD) and allele frequencies (I, D). Specifically, research conducted by Kotaka et al. (2008) on methamphetamine dependence or psychosis reported no significant differences in the genotype and allele frequencies of the CSNK1E gene between methamphetamine-dependent patients and control subjects (31). Similarly, Kobayashi et al. (2011) found no significant differences

in the genotype or allele frequencies of the ADORA1 gene between methamphetamine-dependent/psychotic patients and control subjects (32). While some existing studies have not provided detailed discussions on specific genotypes (II, ID, DD) and allele frequencies (I, D), this may be attributable to the possibility that certain genetic variants do not significantly contribute to the risk of methamphetamine-related disorders in particular populations.

Among individuals with transient and prolonged MAP, genotype II is more commonly expressed in both cases; however, there is an increased frequency of genotype DD in the prolonged cases.

These findings were contradicted by Ezaki et al. (2008), who demonstrated a different pattern. This study examined the role of functional polymorphism in the serotonin transporter gene (5-HTTLPR) in the development of MAP (33). The results indicate a significant genotype association of the 5-HTTLPR polymorphism with MAP, particularly in patients with prolonged psychosis (34). Contrary to the assertion in the question, the frequency of the S allele (not the DD genotype) is significantly higher in patients with prolonged psychosis compared to controls, and even higher in patients with prolonged psychosis and spontaneous relapse (33). Another study revealed that the prolonged use of methamphetamine, combined with a high frequency of the S allele of 5-HTTLPR, can lead to a decrease in serotonin transporter levels and the binding potential of 5-HT(1A) receptors in the brain. This may result in serotonergic system dysfunction, which could contribute to the development of prolonged MAP (33). The contradiction in the research arises because the genetic variants studied differ in the frequency of the II or DD genotype in cases of transient and prolonged MAP. Meanwhile, another study highlighted the 5-HTTLPR polymorphism, particularly the S allele (35, 36), in the development of prolonged MAP; however, both studies focus on MAP (33).

Our study also found that the allele distribution confirmed that the frequency of allele D was significantly higher in cases of prolonged MAP, with significant odds ratios and p-values, indicating the potential role of allele D in the chronicity or persistence of prolonged MAP.

Ezaki et al. (2008) reported that the frequency of the S allele of the 5-HTTLPR polymorphism was significantly higher in patients with prolonged MAP compared to controls. The frequency was even higher in patients with prolonged MAP and spontaneous relapse (33). Similarly, Costa et al. (2009) discussed the D allele in relation to the ACE gene and swimming performance; however, this is not related to MAP. This study found that the D allele was more frequent among elite short-distance swimmers compared to controls. The present study corroborates the evidence for an allelropsychosis-MAP relationship, specifically indicating a higher frequency of allele D in prolonged MAP. In comparison, previous findings identified a different allele, namely the S allele of 5-HTTLPR, as being associated with prolonged MAP (33,37).

These findings indicate that polymorphisms in the NQO2 gene, particularly the D allele, may function as genetic markers for susceptibility to prolonged MAP and the likelihood of spontaneous relapse. The robust statistical associations highlight the potential role of these genes in predicting psychiatric outcomes, especially in cases involving prolonged psychosis and substance use.

Our study found that NQO1 gene polymorphisms may be associated with the development of MAP, spontaneous relapse, and polysubstance abuse and NQO2 gene polymorphisms, particularly the D allele, act as biomarkers for susceptibility to prolonged MAP. Further studies may clarify the mechanisms by which I/D polymorphisms modulate risk, which may provide a genetic basis for personalized therapeutic approaches in managing this condition.

As with any empirical study, this research has limitations. The case-control design allows for a comparative analysis of genetic predispositions associated with methamphetamine dependence and MAP, but it is subject to confounding factors. While demographic variables were matched between patients and controls, additional uncontrolled factors, such as environmental and lifestyle influences, may impact the genetic findings. The analysis of genetic polymorphisms is limited to specific loci and regions examined in this study; other genetic variations may also contribute to susceptibility to oxidative damage associated with methamphetamine dependence. The sample population was confined to individuals in the Makassar region of Indonesia, which may limit the generalizability of the findings to other regions or countries. Lastly, the targeted methodology employed in this study, while effective in identifying differences between clinical subgroups, may obscure other significant differences that could exist between patients and controls. While this study offers insights into the genetic factors associated with methamphetamine dependence and related psychotic disorders, its limitations must be acknowledged when interpreting the results and considering future research in this area.

As a result, this study investigates the relationship between NQO1 and NQO2 gene polymorphisms and MAP within the Makassar population. The NQO1 gene polymorphism demonstrates a significant association with the duration of MAP, with the TT genotype and T allele occurring more frequently in cases of prolonged psychosis. The CT genotype is linked to a higher risk of spontaneous relapse, while the TT genotype is more prevalent among patients with polysubstance abuse. The NQO2 (I/D) gene polymorphism shows a trend towards differential genotype distribution in patients with MAP, with the DD genotype appearing more frequently in prolonged cases and the I allele associated with an increased risk of spontaneous relapse. These findings indicate that polymorphisms in the NQO1 and NQO2 genes may contribute to the susceptibility and clinical manifestations of MAP in the Makassar population.

Ethics Committee Approval: The methodology of this research has been meticulously designed to adhere to the highest ethical and scientific standards, commencing with the approval from the Drug Abuse Ethics Committee of the Faculty of Nursing, Makassar Health Polytechnic. Each participant provided written consent, underscoring their commitment to ethical conduct in genetic research, particularly given the sensitive nature of the DNA analyses involved.

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Use of artificial intelligence: The author does not use artificial intelligence either partially or in whole

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