Addiction & Health

https://ahj.kmu.ac.ir
10.34172/ahj.1593
AHJ. 2025;17: 1593

Original Article

Brain-Derived Neurotrophic Factor Gene Polymorphism, Craving, and Stress Among Alcohol-Dependent Patients: A Preliminary Cross-sectional Study from India

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Abstract

Background: Brain-derived neurotrophic factor (BDNF) plays an important role in neuronal plasticity and survival. The *BDNF* gene *Val66Met* polymorphism is hypothesized to be linked with alcohol dependence syndrome (ADS). We studied the relationship between the *BDNF Val66Met* polymorphism and the clinical features of ADS, including severity, craving, and perceived stress among alcohol-dependent patients.

Methods: In this cross-sectional study on treatment-seeking north Indian male ADS patients aged 18 to 60 years, alcohol dependence severity (Severity of Alcohol Dependence Questionnaire, SADQ), craving (obsessive compulsive drinking scale), and perceived stress (perceived stress scale-4) were measured. The genetic analysis for calculating the *BDNF Val66Met* allele frequency was carried out using TaqMan assays. Statistical analysis was done using SPSS Version 26.

Findings: The participants' mean age (SD) ($n=80$) was 37 ± 8.52 years. Half of the participants had tobacco dependence, too. Almost half of the participants showed alcohol dependence with mild severity. The mean OCDS and PSS-4 scores were 26.08 ± 9.34 and 9.08 ± 2.4, respectively. The allelic frequency of the Val and Met alleles were 73.1% and 26.9%, respectively. Among the Met allele carriers, the OCDS ($P=0.02$) and PSS-4 scores ($P=0.03$) were significantly higher than observed in the Val group patients.

Conclusion: The study concludes that *BDNF* gene *Val66Met* polymorphism could impact clinical variables such as craving and perceived stress in alcohol-dependent subjects. It merits the use of genetic analysis in determining the course of clinical maintenance of alcohol-dependent patients.

Keywords: Alcohol dependence, Brain-derived neurotrophic factor, Craving

Citation: Bagri S, Quraishi R, Kumar R, Singh S, Ambekar A. Brain-derived neurotrophic factor gene polymorphism, craving, and stress among alcohol-dependent patients: a preliminary cross-sectional study from India. *Addict Health*. 2025;17:1593. doi:10.34172/ahj.1593

Received: July 21, 2024, **Revised:** November 4, 2024, **Accepted:** March 12, 2025, **ePublished:** March 15, 2025

Introduction

Brain-derived neurotrophic factor (BDNF) plays a crucial role in neuronal plasticity and survival.[1] The current evidence for BDNF and its relationship with alcohol use is primarily based on animal studies and some human studies. BDNF affects dopamine and serotonin neurotransmitters linked to addiction.[2,3] Dopamine neurons induce BDNF secretion, which controls the expression of dopaminergic D3 receptors in the nucleus accumbens.[4] A non-synonymous polymorphism (rs6265) causes the substitution of valine (Val) to methionine (Met) at position 66 of the proBDNF protein (*Val66Met*). Studies suggest the association of the *Val66Met* polymorphism with altered BDNF secretion and function and increased susceptibility to alcohol dependence syndrome (ADS).[5] In animal studies, the Met allele is linked to decreased BDNF dendritic trafficking, impaired synaptic transmission, and plasticity, suggesting its association with lower BDNF pathway functionality.[6,7] This polymorphism could be linked to higher severity and earlier onset of the disease, a greater risk of delirium tremens, and earlier relapse.[8]

ADS is a global concern.[9] The frequency of the *BDNF Val66Met* genotypes may vary among populations.[10] Alcohol use in India is quite high, where a significant proportion of current drinkers are alcohol dependent. Therefore, it is crucial to understand the various etiological mechanisms behind heavy alcohol consumption and dependence. The *BDNF Val66Met* polymorphism has emerged as a crucial candidate gene in the pathogenesis of ADS over the past decade. However, findings in this field have been equivocal. Thus, it is imperative to study *BDNF Val66Met* polymorphism in the context of ADS across diverse populations. Additionally, the association of *BDNF Val66Met* with clinical parameters, including craving and perceived stress, requires further assessment. To date, there has been no study on the Indian population. This pilot study aimed to measure *BDNF Val66Met* allele frequency in the Indian alcohol-dependent male

population and to explore the association of *BDNF Val66Met* with the clinical features of alcohol dependence.

Materials and Methods

Study setting and participants

This cross-sectional and observational study aimed to assess *BDNF Val66Met* polymorphism among ADS patients seeking treatment at a tertiary care center in North India.

Non-random, purposive sampling was employed to recruit male patients of North Indian ethnicity between 18 and 60 years of age diagnosed with ADS as per ICD-11. Only the patients who gave written informed consent, registered within the past four weeks, and reported having consumed the last dose of alcohol within the past four weeks were included in the study. Patients were excluded if they were unable to understand or respond, were not willing to participate, presented with severe alcohol withdrawal syndrome, psychiatric co-morbidity, or other substance use disorders (except nicotine), had an ethnicity other than North Indian or were prescribed anti-craving medication or deterrent medication for management of ADS in the four weeks prior to the assessment. Ethical approval was obtained from the Institute Ethics Committee before beginning the recruitment of patients (IECPG-133/24.02.2021). Data collection was done between August 2021 and January 2022 by an expert clinician. Two scenarios were considered for sample size calculation. In scenario 1, the genotype frequency was assumed to be unknown (thus set at 50%), and the sample size was estimated to be 97, with a confidence level of 95% and an absolute precision of 10%. In scenario 2, genotype frequency was assumed to be 60.3% (as reported in the Korean study by Pivac et al in 2009),[10] and the sample size was estimated to be 92 with a confidence level of 95% and an absolute precision of 10%. Given feasibility concerns, the proposed minimum sample size was set at 75, resulting in a final sample size of 80.

Sociodemographic and clinical assessments

The sociodemographic and other relevant clinical information was recorded. The Clinical Institute Withdrawal Assessment of Alcohol revised (CIWA-Ar) was used to exclude those who were on severe withdrawal. It is a 10-item clinician-administered scale in the English language used for clinical measurement of alcohol withdrawal severity; its validity and reliability have been established in the Indian population.[11] The Severity of Alcohol Dependence Questionnaire (SADQ) was used to quantify the alcohol dependence severity in the patients. It is a 20-item questionnaire, which includes five subscales, four items in each: physical withdrawal, affective withdrawal, withdrawal relief drinking, alcohol consumption, and rapidity of reinstatement. This scale is available in English, and its validity and reliability have been established in the Indian population. The interpretation of the SADQ based on score included mild (score < 16), moderate (score 16 to 30), and severe (score > 30).[12] The obsessive-compulsive drinking scale (OCDS) was used to assess cravings in patients. This 14-item questionnaire is designed to calculate scores in the obsessive and compulsive domains. This scale is also available in English and has established validity and reliability in the Indian population.[13] The perceived stress scale-4 (PSS-4) measures the stressful situations during one's lifetime. This shortened version of the 10-item PSS scale consists of four questions and is based on a 4-point Likert scale, with the total score ranging between 0 and 16. This scale is available in Hindi and has established validity and reliability in the Indian population.[14,15]

Genetic assessment

A blood sample (5 mL) was collected from the study participants. DNA extraction was performed using a blood DNA extraction kit from Qiagen (QIAamp DNA blood mini kit). The amplification of the *Val66Met* was carried out in a real-time PCR machine, QuantStudio 12 K Flex (Thermo Fisher, India Pvt Ltd). The PCR primers and TaqMan probes were specific to the *Val66Met* (rs6265) (C__11592758_10, Thermo Fisher Life Sciences, India). The primers used: Forward primer: 5′-CTGTCT TGTTTCT GCTTT CTCCCT-3′ and Reverse primer: 5′-ACCCTC ATGGACATG TTTGCA-3'. Genotyping was done using the allelic discrimination assay with QuantStudio 12K flex optical system software. *Val66Met* (rs6265) genotyping was carried out as per our earlier reports.[16] Researchers performing the assay were unaware of the clinical history of the participants.

Statistical analysis

Statistical analysis was done using SPSS version 26 (IBM Corp., 2019). The central tendencies of all variables were calculated using descriptive statistics analysis. Based on their genetic profile, patients were categorized as having the presence and absence of the Met allele. The Shapiro-Wilk test was used to assess if the primary, un-derived dependent variables are normally distributed. Comparative analysis was done using the Mann-Whitney U and chi-square tests to calculate the strength of association between the presence or absence of the Met allele and sociodemographic and clinical variables. Based on genotyping, a sub-analysis was conducted, resulting in the formation of three groups. For the analysis, an ANOVA test was applied. A P value of ≤ 0.05 was considered to be statistically significant.

Results

Sociodemographic profile

A total of 80 ADS patients (all male) were recruited for the study. The mean ± SD of the age of the participants

was 37 ± 8.52 years. The participants were in the 30 to 39 years (45%) and 40 to 49 (32%) years age groups. The majority were married (81%) and unemployed (76%), were living in joint families (60%), and came from urban areas (90%). The sociodemographic profile of the patients is summarised in Table 1.

Substance use and clinical parameters

The substance use pattern indicates half (50%) of the participants were using tobacco in a dependent pattern. Most of them were treatment-naïve, and only 15% had received ADS treatment within the past four weeks. Among those, only 9% had received disulfiram or anti-craving agents in the past.

The SADQ scores indicated that about half of the participants were in the mild category for alcohol dependence severity. The mean OCDS score was 26.08 ± 9.34. The mean PSS-4 score was 9.08 ± 2.4. Table 2 summarizes the substance use-related clinical parameters of the ADS patients.

BDNF (Val66Met) polymorphism and its association with clinical parameters

After performing the allelic discrimination assay, the allelic frequency of the Val and Met alleles was found to be 73.1% and 26.9%, respectively. The genotypic frequency observed among patients was homozygous for 57.5% (Val) and 11.2% (Met), while 31.3% of the patients were heterozygous.

The study participants were allocated to groups based on the presence (Met/Met and Val/Met; $n = 34$) and absence of the Met allele (Val/Val; $n = 46$) to explore the association of BDNF (Val66Met) with the clinical parameters. A comparison between these two groups was carried out (Table 3). A statistically significant difference was seen in the craving ($P = 0.02$) and perceived scores ($P = 0.03$) between the two groups. Among the Met allele carriers, these scores were significantly higher than those of the Met-absent group. No significant difference was observed amongst these groups concerning the severity of alcohol dependence ($P = 16$).

To observe the dose effect of the Met allele, the ADS patients were divided into three groups: Met/Met ($n = 9$), Val/Met ($n = 25$), and Val/Val ($n = 46$). The comparison of scores on craving and perceived stress between the three groups is summarised in Table 4. Following analysis, it was found that the craving, as presented as OCDS total ($P = 0.01$), obsessive ($P = 0.02$), and compulsive ($P = 0.02$) scores, was statically higher among the Met allele carriers, indicating a dose-dependent effect. The homozygous or heterozygous Met allele carriers are observed to score higher on their perceived stress stores (PSS-4). However, the results were not significant ($P = 0.07$). No significant difference was noticed in the severity of alcohol dependence ($P = 0.42$) between these three groups.

Table 1. Sociodemographic profile of ADS patients (n = 80)

Variables	Mean	SD
Age	36.99	8.52
Monthly income (INR)	31825.00	27902.53
	Group	**n (%)**
Marital status	Married	65 (81.25)
	Never married	11 (13.75)
	Other	4 (5)
Occupation	Employed	19 (23.75)
	Unemployed	61 (76.25)
Education	Illiterate	2 (2.50)
	Primary	15 (18.75)
	Secondary	36 (45)
	Graduate	27 (33.75)
Current living arrangement	Joint family	48 (60.00)
	Nuclear family	32 (40.00)
Residence	Urban	72 (90.00)
	Rural	8 (10.00)

Table 2. Substance use and clinical parameters of ADS Patients ($n = 80$)

Variable	Mean (SD)/*n* (%)
Age at onset (years)	22.32 (5.61)
Duration of use (years)	14.81 (8.72)
Age at dependence (years)	27.45 (6.9)
Dependent use (years)	9.68 (8.87)
Severity of alcohol dependence	
Mild	40 (50.00%)
Moderate	21 (26.25%)
Severe	19 (23.75%)
Usual amount (standard drinks/day)	13.63 (9.61)
Type of alcohol consumed mostly	
IMFL	50 (62.5%)
CML	30 (37.5%)
Family history of alcohol use disorder	21(26.25%)
History of treatment of ADS	12 (15%)
Medical complications due to alcohol use	53 (66.25%)
History of tobacco dependence	40 (50.00%)
Age at onset (years)	20.6 (5.99)
Duration of use (years)	17.45 (10.76)
Age at dependence (years)	21.6 (5.63)
Dependent use (years)	16.94 (10.88)
Family history of tobacco dependence	10 (12.50%)
PSS-4 score mean (SD)	9.08 (2.4)
OCDS mean (SD)	
Obsessive subscale	12.13 (4.95)
Compulsive subscale	13.95 (4.59)
OCDS total	26.08 (9.34)

Table 3. The *BDNF* (*Val66Met*) and clinical parameters of ADS Patients ($n = 80$)

Variable *n* (%) Mean rank (sum of rank)		Met allele 34 (42.5%)	Val allele 46 (57.5%)	Test stats (*P* value)
OCDS	Total	47.25 (1606.5)	35.51 (1633.5)	552.5 (0.02)*
	Obsessive subscale	46.18 (1570.0)	36.30 (1670.0)	589.0 (0.06)
	Compulsive subscale	48.03 (1633.0)	34.93 (1607.0)	526.0 (0.01)*
SADQ total		45.54 (1548.5)	36.77 (1691.5)	610.5 (0.09)
PSS-4		46.76 (1590.0)	35.87 (1650.0)	569.0 (0.03)*

* Mann-Whitney U test significant value.

Table 4. Dose effect of the Met allele on clinical parameters of ADS patients ($n = 80$)

Variable *n* (%) Mean (SD)		Met/Met 9 (11.2%)	Val/Met 25 (31.2%)	Val/Val 46 (57.5%)	Test stats (*P* value)
OCDS	Total	33.88 (5.77)	27.48 (8.27)	23.80 (9.59)	6.36 (0.003)*
	Obsessive subscale	17.00 (3.24)	12.48 (4.57)	11.00 (4.89)	4.25 (0.018)*
	Compulsive subscale	16.88 (2.66)	15.00 (3.94)	12.80 (4.87)	5.32 (0.007)*
PSS-4		9.0 (2.48)	9.48 (2.70)	8.54 (2.32)	3.75 (0.028)*

* Analysis of variance (ANOVA) significant value.

Discussion

ADS has a 50% genetic concordance[17]. BDNF is crucial in the molecular pathophysiology of alcohol dependence, influencing neural plasticity, stress response, and reward pathways, with changes in BDNF linked to the reinforcement of the addictive properties of alcohol[18]. Alcohol triggers dopamine release in the mesolimbic pathway, reinforcing the pleasurable outcome of drinking. Chronic alcohol use disrupts BDNF levels in this pathway, particularly in the ventral tegmental area (VTA) and the nucleus accumbens regions, central to reward processing. This dysregulation of BDNF can impair neuroplasticity in these areas, perpetuating compulsive drinking behavior.[19,20] Chronic alcohol consumption leads to lower BDNF levels in areas such as the prefrontal cortex and the hippocampus, leading to heightened stress sensitivity and impaired stress-coping mechanisms. Reduced BDNF exacerbates stress reactivity, making it challenging for individuals to handle stress without resorting to alcohol, thus sustaining the cycle of dependence.[21,22] BDNF promotes synaptic plasticity and neurogenesis, which are critical for learning and memory. Long-term alcohol exposure reduces BDNF, especially in the hippocampus, impeding the brain's ability to form new connections. This reduction leads to cognitive deficits that can maintain addiction by diminishing self-control and decision-making capacity.[6]

This exploratory study was conducted to assess the association between *BDNF Val66Met* and the clinical parameters linked with alcohol dependence in the North Indian male population. The *BDNF* gene's *Val66Met* polymorphism was selected due to its role in intracellular trafficking, proBDNF packaging, and secretion of BDNF.[6] Some studies associated the Met allele with increased alcohol consumption, violent behavior, and a greater incidence of delirium.[23,24] However, other studies with similar objectives did not report a significant difference.[25-27] In our study, there was no statistical difference in the amount of alcohol consumed, medical complications caused by alcohol use, and family histories of alcohol use between the Met allele carrier and non-carriers. These findings can be explained by the multifactorial etiology of ADS, involving multiple genes or factors, while in our study, we only assessed the *BDNF Val66Met* gene polymorphism.[28] It is possible that the participants are not representative of the general population. In one study, it was observed that those who had the *COMT Met158Met* and *BDNF Val66Val* genotypes consumed more alcohol than people who had the other variations of these genes ($P = 0.039$).[29] The authors proposed that the combined effects of the *COMT* and *BDNF* genes on the dopaminergic response to alcohol were responsible for this discovery. Earlier, the authors worked on the catechol-O-methyl transferase gene (*COMT Val158Met*) and reported significantly higher consumption of alcohol among ADS patients who were Met carriers.[30]

In our study, participants with the Met allele reported significantly more craving. Preclinical studies have displayed the association of the Met allele with impaired intracellular trafficking and secretion of BDNF.[31] Appropriate levels of BDNF are required for optimal performance of the serotonin and dopamine systems. Reduced dopamine and serotonin neurotransmitter levels lead to increased craving.[32,33] A preclinical study using mice with Met homozygous mutation reported excessive and compulsive amounts of alcohol consumption. This drinking pattern stopped by administering the tropomyosin receptor kinase B agonist or introducing the Val allele.[8] Another study found that mice with the Met allele developed a liking for alcohol compared to social interaction.[34] In addition, other parameters that could indicate the severity of craving, such as the amount of

alcohol consumed per week, have been measured. Some studies have consistently reported that those with the Met allele had significantly higher alcohol use.[23,29,35] Therefore, the *BDNF* Met allele might play a role in substance-related cues after withdrawal in alcohol-dependent individuals. The association between *BDNF* gene polymorphism and objective craving measurement in human participants has been reported for the first time. Others have assessed the relationship between serum BDNF levels and craving for alcohol. Few human studies have observed no relation between serum BDNF levels and craving for alcohol.[36-39] Overall, the literature points out that BDNF is crucial in the development of a craving for alcohol. Future studies should investigate the role of BDNF in the development of AUD and the development of craving for alcohol.

The *BDNF Val66Met* is important in stress vulnerability in those with ADS. The study group containing the Met allele perceived significantly greater stress. The literature indicates that lower expression of BDNF might be linked to increased HPA axis activity and increased sensitivity to stress.[40,41] Additionally, animal studies indicate that early childhood stress may lead to decreased BDNF expression, which leads to atrophy and degeneration of neurons in the hippocampus and cortex.[41] An earlier study cited that during physical stress, such as in the cold press test, those with the Met allele reported higher anticipatory responses and anxiety, implicating the role of the *BDNF* gene in the stress vulnerability of an individual.[23] However, the association between *Val66Met* polymorphism and ADS is inconsistent.[27] A metanalysis reports a pooled odds ratio that does not support a consistent association of this polymorphism with ADS.[42]

Our study has several limitations. It is a cross-sectional pilot study constrained by the small sample size. In addition, the study's power was inadequate. A preliminary power analysis could not be done as we lack precise information regarding the prevalence of the *BDNF Val66Met* genotype in the Indian population with ADS. Another feature that is simultaneously a limitation (as well as a strength) is that we used a homogenous group of North Indian males seeking treatment at tertiary care facilities. This limits generalizability considering the diverse genetic profile of the Indian population. On the other hand, a less diverse study sample has the advantage of analyzing a more homogenous group, thereby increasing the statistical power despite the low sample size. In addition, the sample was restricted to men, so the association in women remains unknown. We assessed alcohol consumption only among treatment-seeking participants with ADS, thus inadvertently excluding individuals with heavy drinking not amounting to alcohol dependence. Given the high rate of co-morbidity between alcohol use and tobacco use, we did not exclude those who had concurrent tobacco use with any consumption pattern. However, the allelic sub-groups did not differ in tobacco use rates. Data on sociodemographic variables and clinical variables related to substance use were based on the self-report only. We only studied the *BDNF Val66Met* (*rs6265*) polymorphism, but other *BDNF* polymorphisms (*rs13306221* and *rs16917204*) may not be significantly linked with alcohol dependence.[43]

Conclusion

This exploratory study reveals an association between the *BDNF Val66Met* gene polymorphism and clinical parameters linked to ADS in the North Indian male population. Although our findings did not show significant differences in alcohol consumption or medical complications between individuals with or without the Met allele, those with the Met allele reported higher levels of craving and perceived stress. These results are consistent with existing literature, suggesting that the Met allele may hamper intracellular trafficking and BDNF secretion, both vital for dopamine and serotonin functions related to features of addiction.

The increased perception of stress in Met allele carriers suggests a connection between BDNF expression and hypothalamic-pituitary-adrenal (HPA) axis activity. However, the study is bound by limitations, including a small sample size, the selection of a homogeneous group, and the reliance on self-reported data for the sociodemographic and clinical variables, which introduces inherent limitations.

Future studies should investigate the role of BDNF in the development of alcohol use disorder (AUD) and cravings, utilizing larger, more diverse populations and employing case-control designs and longitudinal measures. Additionally, examining the combined impact of the *Val66Met BDNF* polymorphism and other genetic variations, such as the *COMT Val158Met* polymorphism, along with genome-wide association studies (GWAS), will help us understand the genetic and environmental factors contributing to alcohol dependence. This comprehensive approach will provide deeper insights into the neurobiological mechanisms underlying ADS.

Acknowledgments

The authors hereby express their gratitude to the staff at the National Drug Dependence Treatment Centre (NDDTC), AIIMS New Delhi for their support.

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Competing Interests
The authors have no conflict of interest.

Funding
Nil.

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