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Association of BDNF *Val*^{66}*Met* polymorphism with Amphetamine and Opioid dependency in Azeri population of Iran: A case- control study

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Abstract

Background: Emerging evidence suggests a link between the Val66Met polymorphism of brain-derived neurotrophic factor (BDNF) and an increased risk of neurobehavioral disorders (reference here). The present study aims to elucidate the potential relationship between this genotype and the predisposition to amphetamine and opiate dependencies among the Iranian Azeri population. Through rigorous analysis and comprehensive genetic profiling, this research contributes valuable insights into the complex interplay between genetic factors and substance dependency in this ethnic group.

Methods: A cohort of 150 participants was recruited for this study, consisting of 133 males and 17 females in the treatment group, alongside 100 controls, comprising 74 males and 26 females—genotyping procedures utilized PCR-RFLP genotyping.

Results: Comprehensive analysis revealed no statistically significant differences in the distribution of genotypes and alleles of the BDNF gene polymorphism (rs6265) between the case and control cohorts. The control group's GG and AA genotypes were higher than the case group's, while the control group's AG genotype was lower than the case group's, but a statistically significant difference was not shown ($P > 0.05$).

Conclusion: The outcomes of this rigorously designed study fail to substantiate a significant correlation between the *Val66Met* polymorphism of the BDNF gene and the susceptibility to amphetamine and opiate dependency. This finding adds a new piece of the puzzle to our understanding of genetic predispositions in substance dependence.

Keywords: Amphetamine; Addiction; BDNF gene; Opiate; *Val66Met*.

1. Background

Substance use disorder represents a pervasive global challenge marked by the persistent pursuit of substances despite adverse outcomes, detrimentally affecting cognitive functions such as learning and memory. Genetic variations play a pivotal role

in both the onset and likelihood of relapse in substance dependency (1). Brain-derived neurotrophic factor (BDNF), a neurotrophin growth factor, exerts widespread influence throughout the Central Nervous System (CNS), governing critical processes including development, survival, differentiation, and synaptic plasticity. Furthermore, neurotrophin proteins, including BDNF, intricately regulate neural activity within the nervous system (2). This activity-dependent remodeling is deemed essential in the transition from casual substance use to substance dependence. Exploring the pivotal role of BDNF in substance dependence further elucidates this intricate interplay (3, 4).

The BDNF gene encodes a pre-proprotein that undergoes alternative splicing to yield a mature protein belonging to the nerve growth factor family. Synthesized within the endoplasmic reticulum (ER), BDNF is sorted in the Golgi apparatus and cleaved into mature BDNF, intracellularly or extracellularly, resulting in a 14 kDa protein. BDNF can be transported to its target neurons anterogradely (5, 6) after synthesis. This protein binds to its receptor within the adult brain, exerting crucial effects on neuronal survival and playing a well-documented role in regulating mood disorders (7). Evidence suggests that BDNF is implicated in amphetamine dependence, as studies have demonstrated an increase in striatal BDNF levels following methamphetamine injection in mice (8).

Numerous genetic investigations into addictive disorders have unveiled polymorphisms that wield influence over initial susceptibility, signaling the intricate interplay between genetic factors and addictive behaviors (9-11). However, it is increasingly recognized that genetic influences may extend beyond mere susceptibility, exerting effects across multiple stages of the addiction cycle (12, 13). Despite this nuanced understanding, the direct modification of addictive behaviors by functional biological genotypes remains inadequately supported by current evidence (14).

Exploration into the role of brain-derived neurotrophic factor (BDNF) has emerged as a focal point in understanding substance abuse (15), with studies indicating its potential correlation with the behavioral response to psychomotor stimulants. BDNF's involvement in modulating neurotransmitters associated with substance abuse underscores its significance as a promising candidate for further investigation into addictive behaviors. Additionally, insights gleaned from animal research underscore BDNF's regulatory influence over dopaminergic and serotonergic functions, crucial components intricately tied to the mechanisms of substance addiction (16).

A pivotal single nucleotide polymorphism (SNP) situated at codon 66 of the brain-derived neurotrophic factor (BDNF) gene (rs6265) precipitates a consequential valine-to-methionine substitution, exerting pronounced effects on the activity-dependent secretion of BDNF and the intracellular levels thereof. This SNP intricately modulates the intracellular concentration of pro-BDNF and orchestrates the secretion dynamics of the mature peptide while preserving the functional integrity of the mature BDNF protein (17, 18).

Furthermore, BDNF emerges as a multifaceted peptide with notable implications in modulating dopamine signaling, implicating its involvement in governing the intricate reward pathway associated with nicotine addiction (19, 20). Cumulative evidence underscores a discernible correlation between genetic variants of BDNF and the manifestation of nicotine addiction, particularly among male smokers of European-American lineage, illuminating the complex interplay between genetic predisposition and addictive behavior. Furthermore, a potential association between BDNF polymorphism and methamphetamine dependence, including

susceptibility to methamphetamine psychosis, has been highlighted by emerging research. Notably, among Taiwanese individuals diagnosed with methamphetamine dependence, a significant correlation was identified between the presence of methamphetamine dependence and the *Val66Met* BDNF gene polymorphism (p=0.046). This observation suggests that individuals homozygous for the 196G allele may manifest an elevated vulnerability to methamphetamine dependence (21, 22).

The principal aim of this investigation is to elucidate the plausible correlation between amphetamine and opioid addiction and a specific BDNF gene polymorphism. To corroborate its relevance to the predisposition to substance addiction, a distinct single nucleotide polymorphism (SNP), previously associated with susceptibility to substance addiction, was meticulously scrutinized within the Iranian populaces (18).

2. Methods

Population

In the population section, one hundred and fifty individuals diagnosed with amphetamine and opioid dependence were selected from the rehabilitation clinic at Razi Mental Hospital (RMH), Tabriz University of Medical Sciences (TUMS), Iran.

The participants, comprising 133 adult men and 17 adult women, with an age range of 36 ± 10 years, were included based on DSM-5 and ICD-10 criteria for drug dependence. The selection process involved a clinical interview conducted by two experienced psychiatrists and a questionnaire to collect information on the type of substance use disorder and its behavioral impact. Individuals with severe psychiatric disorders were excluded from the study.

The reference group, consisting of 74 men and 26 women with an age range of 41.2 ± 16.1 years and no history of substance use or psychiatric disorders, was chosen from the same hospital. The ethical review board of TUMS approved the study protocol.

DNA Extraction plus Genotyping

In the DNA extraction and genotyping section, approximately 5 milliliters of peripheral blood was meticulously collected from each participant and diligently preserved at -20 degrees Celsius for subsequent meticulous analysis. The extraction of genomic DNA was conducted with utmost care and precision, employing the well-established salting-out method. Following this meticulous extraction process, genotyping was meticulously carried out utilizing the sophisticated polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique.

A precise 216 base pair (bp) segment of the BDNF gene was meticulously amplified using meticulously designed forward (5’-CCAGGTGAGAAGAGTGATG-3') and reverse (5’-AGTCTGCGTCCTTATTGTT-3') primers. The PCR reaction mixture, meticulously prepared to ensure accuracy and reproducibility, consisted of 10X reaction buffer, two mM MgCl2, 0.2 mM dNTPs, 1x forward and reverse primers, 0.1-0.5 µg DNA, and 1.0 U of Taq polymerase. The amplification process was meticulously conducted for 35 cycles, commencing with an initial denaturation step at 95 degrees Celsius(°C) for 5 minutes(min), followed by denaturation at 95°C for 30 seconds(s), annealing at 65°C for 30 s, extension at 72°C for 45 s, and a final extension at 72°C for 5 min.

After the meticulous PCR amplification, the resulting products underwent precise treatment with the restriction enzyme PmlI (Eco72I) and were subjected to electrophoresis on 2.5% agarose gels. The resultant fragments were then meticulously visualized and analyzed with meticulous attention to detail (Figure 1).

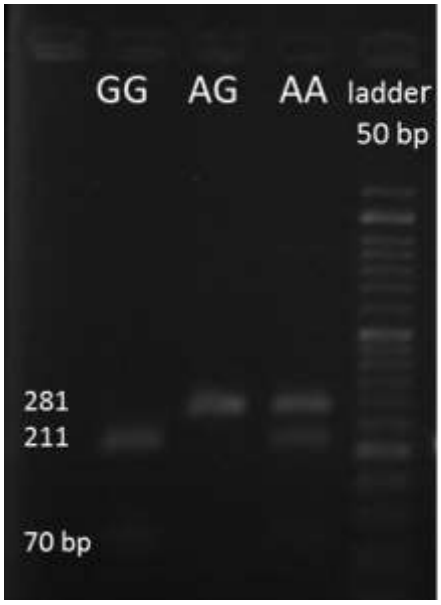

Figure 1: illustrates the PCR-RFLP outcomes for the BDNF rs6265 polymorphism

3. Results

In pursuit of unraveling the potential nexus between the Val66Met polymorphism (rs6265) of the BDNF gene and the susceptibility to amphetamine and opioid abuse, a cohort comprising 150 patients grappling with addiction issues and 100 healthy individuals was meticulously assembled for this investigation.

The assessment of Hardy-Weinberg equilibrium yielded no discernible deviations of statistical significance between the patient and comparison cohorts. Noteworthy was the observation that while the frequencies of the GG and AA genotypes skewed higher within the comparison group as opposed to the patient cohort, conversely, the AG genotype exhibited reduced prevalence within the Reference group. Despite these disparities, statistical significance remained elusive, with p-values exceeding the threshold of 0.05. A comprehensive breakdown of these findings is meticulously outlined in Table 1.

Regarding allele distribution, the patient cohort displayed BDNF A and G allele frequencies of 16.66% and 83.33%, respectively, while their counterparts in the comparison group exhibited 14% and 86%, respectively. However, despite these numerical discrepancies, no substantive disparity of statistical significance was observed between the two cohorts, with p-values surpassing the predetermined threshold of 0.05. For a comprehensive overview of our meticulous findings, we encourage readers to peruse Table 1.

Table 1: BDNF Gene Polymorphism: Genotype and Allele Distribution

BDNF	Case (%)	Control (%)	OR (95% CI)	P value
Genotype				
AA	4 (2.66 %)	3 (3%)	0.884 (0.128-5.911)	0.885
AG	42 (28 %)	22 (22%)	1.379(0.690-2.760)	0.327
GG	104 (69.33 %)	75 (75 %)	0.754(0.386-1.467)	0.371
total	150	100		
Allele				
A (Met)	50 (16.66 %)	28 (14 %)	1.229 (0.533-2.846)	0.6
G(Val)	250 (83.33 %)	172 (86%)	0.814 (0.351-1.878)	0.6

Abbreviations: CI, confidence interval; OR, odds ratio. Values are presented as frequencies (percentages).

5. Discussion

Brain-derived neurotrophic factor (BDNF) is one of the most extensively investigated psychomotor stimulants within the central nervous system. Its multifaceted actions encompass promoting the growth, differentiation, and survival of nascent neurons (23-25). Additionally, BDNF has been implicated in augmenting midbrain dopamine release (26), facilitating long-term potentiation, which underpins synaptic stability (27-29), and potentially contributing to the development of addictive behaviors (30, 31). In the context of substance use disorders, BDNF appears to play a critical role in the rewarding and reinforcing aspects of drug use.

A compelling body of evidence derived from both meticulously controlled laboratory experiments (in vitro) and investigations utilizing living organisms (in vivo) underscores a robust association between prolonged drug exposure and alterations in BDNF levels within animal models (32, 33). Notably, the administration of BDNF in healthy rats has been shown to induce behaviors characteristic of opiate dependence, highlighting a potential causal role for BDNF in addiction development (34, 35). Furthermore, a substantial body of prior research has documented a noteworthy association between the BDNF rs6265 polymorphism and susceptibility to addiction across various substances, including alcohol, heroin, methamphetamine, and nicotine.

Individuals carrying the BDNF mutant allele (66Met) have been shown to exhibit reduced BDNF secretion, leading to diminished neurotrophic effects. We hypothesized that the 66Met allele might be associated with either:

Enhanced Resilience: An increased capacity to resist environmental or pharmacologically induced changes in drug-seeking behavior.

Diminished Behavioral Adaptability: A reduced ability to modify behavior, particularly in advanced stages of addiction.

This study investigated the potential association between the *Val66Met* polymorphism (rs6265) of the BDNF gene and amphetamine or opioid dependence in Iranian-Azeri patients. Our primary objective was to evaluate whether single nucleotide polymorphisms (SNPs) within the BDNF gene influence this population's susceptibility to drug dependence.

Analysis of BDNF genotype and allele frequencies in individuals with substance dependence revealed no statistically significant differences compared to the reference group ($p > 0.05$; see Table 1). While a trend emerged with a higher prevalence of the AG-heterozygous genotype in the treatment group, the AA (Met/Met) and GG homozygous genotypes were more prevalent in the controls. However, despite these trends, genotype analysis yielded no significant difference in the Val66Met (G196A) variant distribution between healthy controls and substance-dependent patients.

Our investigation revealed a trend towards a higher prevalence of the *66Met* allele within the treatment group compared to the Reference group (OR = 1.229). Notably, the Met allele emerged as the predominant allele in the BDNF *Val66Met* polymorphism among individuals with substance dependence. However, despite this trend, statistical analysis yielded no significant difference in the overall distribution of Met and Val allele frequencies between the two groups.

This is not the first exploration into the potential association between the *Val66Met* variants and heroin use disorder (HUD) (36-39). A recent meta-analysis suggests that the Val allele may be a risk factor for heroin dependence, with a higher frequency of Val carriers observed among Han Chinese heroin abusers (34, 36).

Interestingly, Cheng et al. (2005) reported a contrasting finding, suggesting that individuals carrying the Val allele initiate heroin abuse at a later stage compared to those with the Met allele (36).

To comprehensively comprehend the role of the BDNF *Val66Met* polymorphism in drug-seeking and use behaviors within East Asian populations, further research is imperative. A broader investigative scope encompassing a wider variety of addictive substances is crucial. This will determine if the genotype's influence on addiction transcends specific drug classes. Notably, Haerian's meta-analysis identified the rs6265 polymorphism as a potential risk factor for methamphetamine dependence in South Asians and heroin dependence in the Chinese population, highlighting potential population-specific effects (40).

Our findings resonate with a previous study conducted by Itoh et al.[14,] who reported no significant association between the BDNF *Val66Met* polymorphism and methamphetamine abuse in a Japanese population. This similarity underscores the need for further investigation into potential moderating factors, such as ethnicity (41).

Sim et al. (42) explored the relationship between the *Val66Met* polymorphism and methamphetamine addiction in a Malaysian population, revealing an association, particularly among Chinese individuals, but not among other ethnicities (42, 43). This finding highlights the potential influence of ethnicity on the BDNF *Val66Met* polymorphism's association with addiction.

The discrepant results across these studies underscore the complex interplay between genetics and environmental factors, including ethnicity, in shaping susceptibility to substance use disorders. Future research incorporating larger, ethnically diverse samples must elucidate the nuanced influence of the BDNF *Val66Met* polymorphism and its potential interaction with ethnicity in East Asian populations.

6. Conclusion

Our investigation did not unveil a statistically significant association between the Val*66*Met polymorphism of the BDNF gene and susceptibility to amphetamine and opioid dependence in the Iranian-Azeri population. This finding contributes to the expanding body of research with disparate results concerning the *Val66Met* polymorphism and addiction.

In order to achieve a more comprehensive understanding of BDNF's role in substance use disorders, future studies should consider the following avenues:

1. Exploration of Gene-Gene Interactions: Potential interactions between the *Val66Met* polymorphism and other pertinent BDNF gene variants should be investigated. Analyzing a broader spectrum of BDNF polymorphisms within a larger cohort could elucidate more nuanced genetic influences on addiction susceptibility. 2. Heterogeneity of Substance Use Disorders: The scope should be expanded to encompass a broader range of addictive substances. This will determine if the *Val66Met* polymorphism's influence transcends specific drug classes. By including individuals with diverse substance use disorder diagnoses, researchers can assess the generalizability of these findings. 3. Ethnically Diverse Populations: Participants from various ethnic backgrounds should be recruited, considering the potential influence of ethnicity highlighted by previous studies.[42,43] Studies with ethnically diverse samples can provide a more complete picture of the interplay between genetics and ethnicity in addiction.

Future research can shed greater light on the complex interplay between BDNF genetics and substance use disorders. Furthermore, such endeavors have the potential to identify novel biomarkers for addiction risk assessment and the

development of more targeted treatment strategies.

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Conflicts of interests: The authors declare that there are no competing interests.

Consent for publication: Not applicable.

Ethics approval and consent to participate: This study was conducted according to the principles of the Helsinki Declaration. All participants' information remained completely anonymous. This research protocol was approved by the ethics committee of Tabriz University of Medical Sciences (code no. 5/4/12152). The study was conducted under the principles of the Declaration of Helsinki.

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Author contributions: LMF, NZ, and SD contributed to the study design and lab experiments. SA, HB, and SD performed statistical analyses and interpretation of data. SA & AM supervised the study and contributed to all parts of the paper. LMF wrote the paper; all authors read and approved the final version.

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