Research article

Assessment of the role of zinc finger protein-804a (znf804a) (rs1344706) gene polymorphism in schizophrenia and methamphetamine addiction patients

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(Received: April 2023 Revised: May 2023 Accepted: June 2023)

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ABSTRACT

Introduction and Aim: The zinc finger protein 804A (ZNF804A) gene has garnered significant interest as a gene associated with an increased risk of psychosis. This interest stems from the strong association observed between a specific single nucleotide polymorphism (SNP), namely rs1344706, within the ZNF804A gene, and various psychosis phenotypes, including schizophrenia and bipolar disorder. In this study, we aimed to assess the functional impact of ZNF804A gene polymorphism in individuals diagnosed with schizophrenia and methamphetamine addiction.

Materials and Methods: This nested case control research included 50 individuals with schizophrenia and 50 methamphetamine (crystal) users recruited from Ibn-Rushed Psychiatric Teaching Hospital in Baghdad. 50 healthy subjects were also recruited as a control group. All participants were subjected to thorough physical examination. The serum concentration of Zinc Finger Protein-804A (ZNF804A) was determined using a sandwich enzyme-linked immunosorbent assay. Genomic DNA was isolated from whole blood samples, and the Taqman allelic discrimination method was used to genotype the ZNF804A gene rs1344706 polymorphism.

Results: Patients with schizophrenia had a significantly higher median level of ZNF804A (48.67 ng/L) than controls (25.56 ng/L) or methamphetamine users (35.62 ng/L). The SNP rs1344706 homozygous (AA) genotype was more common in schizophrenia patients (36% vs. 16%) and methamphetamine addiction patients (4%), with significant differences (OR= 1.32, 95%CI= 1.32-11.75, p=0.014 and OR= 11.7, 95%CI=02.43-56.4, p=0.002, respectively).

Conclusion: The AA genotype of rs1344706 polymorphism could be considered a risk factor for schizophrenia but has a protective role against methamphetamine addiction. Serum level of ZNF804A could be used to confirm the diagnosis of schizophrenia in young individuals with subtle clinical features.

Keywords: Finger Protein-804A (ZNF804A); SNP rs1344706; Schizophrenia; Methamphetamine addiction.

INTRODUCTION

Schizophrenia continues to pose a significant burden on global society. According to data derived from the worldwide Burden of Disease Study, mental and behavioral disorders contribute to 7.4% of the disability-adjusted life year (DALY) burden worldwide, with schizophrenia alone accounting for 0.6% (1). Our understanding of schizophrenia's development has largely been shaped by the neurodevelopmental theory initially elucidated by Weinberger (2).

The zinc finger protein 804A (ZNF804A) gene has gained particular attention due to its association with an increased risk of psychosis. Encoded by this gene, the ZNF804A protein is primarily located in the cytoplasm and neurites within the human cortex. It exhibits expression in various types of neurons, such as pyramidal, dopaminergic, GABAergic, and Purkinje neurons in the mouse brain. Notably, when the expression of the ZNF804A gene is reduced, a significant decrease in neurite outgrowth and dendritic spine density is observed in cortical neurons. These findings suggest a critical role of ZNF804A in the maturation and outgrowth of neurites (3).

The ZFP804A gene exhibits polymorphism, and a comprehensive multistage association analysis has identified a specific single nucleotide polymorphism (SNP), rs1344706, situated within the second intron of the ZNF804A gene. This polymorphism has been found to have a significant correlation with a wider range of psychosis-related conditions, including schizophrenia and bipolar disorder (4). Moreover, research has demonstrated that SNP rs1344706 plays a role in modifying the connection between a widely recognized environmental risk factor for psychotic disorders, such as cannabis, and schizotypal traits in mentally healthy adult individuals (5). The present study intended to evaluate the functional impact of ZNF804A SNP in schizophrenic and methamphetamine addicts.

MATERIALS AND METHODS

This is a case control study that was conducted on a sample of 50 patients with schizophrenia and 50 patients of methamphetamine (crystal) addiction

patients recruited from Ibn-Rushed Psychiatric Teaching Hospital in Baghdad city. The diagnosis of schizophrenia was performed by specialist psychiatrists depending on the examination criteria in Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in addition to cognition and memory tests approved by the hospital as diagnostic aid. The diagnosis of methamphetamine addiction was made by specialist psychiatrists depending on clinical data and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) criteria of addiction (6). Fifty apparently healthy subjects were recruited randomly from private clinics to serve as control group. All participants underwent a comprehensive physical examination and investigations, which encompassed assessments of age, gender, body mass index (BMI), lipid profile, and complete blood count. The study received approval from the Institutional Review Board at the College of Medicine-Al-Nahrain University (IRB No. 146: Date: 4/4/2021). Prior to their involvement, written consent was obtained from all participants.

About 5 mL of blood was gathered from all participants, of which 2 mL was transferred to a tube containing ethylene-diamine tetra acetic acid (EDTA) and the remaining 3ml was transferred to a gel tube for separating out sera. Serum separated was stored in Eppendorf tubes and stored at -20ºC until use. Sandwich Enzyme-Linked Immunosorbent Assay (ELISA) (Sunlo, China) was used for measuring the serum concentration of ZNF804A following the manufacturer's protocols

Genomic DNA was isolated from the whole blood samples using the standard extraction method. The genotyping of ZNF804A gene was conducted utilizing the Taqman allelic discrimination method on the 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA).

To confirm the presence of cognitive impairment in all patients, they underwent assessment using the mini-mental state examination (MMSE). The MMSE score was integrated into the Diagnostic Interview Schedule as a means to evaluate cognitive impairment consistently across all patients. The MMSE is a comprehensive tool utilized for assessing mental status. The assessment tool consists of 11 items designed to evaluate cognitive abilities across five domains: orientation, registration, attention and calculation, recall, and language. The maximum achievable score on this tool is 30, with a score below 25 indicating possible impairment. Additionally, a cutoff value of 23 has proven effective in distinguishing individuals with confirmed cognitive impairment from those who are healthy (7). The MMSE takes only 5-10 minutes to administer and is therefore used repeatedly and routinely.

Statistical analysis

The obtained data was subjected to statistical analysis using SPSS program version 25. Figures were created using GraphPad Prism 6. Normality tests (the Shapiro-Wilk test) were performed on continuous data to determine their distribution. Data following a normal distribution were expressed as mean with standard deviation and analyzed using one-way analysis of variance. On the other hand, non-normally distributed data were presented as median and range, and analyzed using the non-parametric Kruskal-Wallis test. Categorical variables as well as the deviation of rs1344706 genotypes from Hardy Weinberg Equilibrium (HWE) were analyzed with Chi square. To assess the relationship between the rs1344706 polymorphism and schizophrenia as well as methamphetamine addiction, a binary logistic regression test was conducted. The test yielded the odds ratio (OR) along with its corresponding 95% confidence interval (CI). A p-value below 0.05 was deemed statistically significant.

RESULTS

With respect to gender, control group included 36 (72.0 %) males and 14 (28.0 %) females, schizophrenia group included 24 (48.0 %) males and 26 (52.0 %) females and methamphetamine group included 44 (88.0 %) males and 6 (12.0 %) females and with a significant difference ($p < 0.001$). Regarding age, there was a notable discrepancy in the average age across the study groups ($p < 0.001$). The mean age of the methamphetamine group was significantly lower than that of both the control group and the schizophrenia group. However, there was no significant distinction in mean age between the control group and the schizophrenia group. Concerning mini-mental status, the levels in control group was 25.60 ±1.50, that of Schizophrenia group was 19.12 ±1.90 and that of methamphetamine group was 18.84 ±1.75 and the difference in MMS between different groups was significant ($p< 0.001$) as patients in both schizophrenia and methamphetamine group demonstrated significantly lower MMS than control group. However, there was no significant difference between schizophrenia and Methamphetamine group.

Serum level of Zinc Finger Protein-804A

With respect to serum Zinc Finger Protein-804A (ZNF804A) levels, there was significant variation in ZNF804A between groups ($p = 0.046$). It was highest in the schizophrenia group in comparison to both control group and methamphetamine group; but there was no significant difference between control and Methamphetamine group (Fig. 1).

Table 1: Demographic characteristics of patients and control subjects enrolled in this study

Characteristic	Control *n* = 50	Schizophrenia *n* = 50	Methamphetamine *n* = 50	*P value*
Age (years) Mean ±SD Range	 37.34 ±8.97[a] 22 -57	 37.24 ±12.48[a] 19 -62	 27.36 ±6.71[b] 20 -50	 < 0.001 O**
Gender Male, *n* (%) Female, *n* (%)	 36 (72.0 %) 14 (28.0 %)	 24 (48.0 %) 26 (52.0 %)	 44 (88.0 %) 6 (12.0 %)	 < 0.001 C**
MMS Mean ±SD Range	 25.60 ±1.50[a] 24 -29	 19.12 ±1.90[b] 16 -23	 18.84 ±1.75[b] 16 -22	 < 0.001 O**

SD: standard deviation; **O**: one way ANOVA; **C**: chi-square test; **: significant at $p < 0.01$; Small letters indicate significance difference following post hoc test.

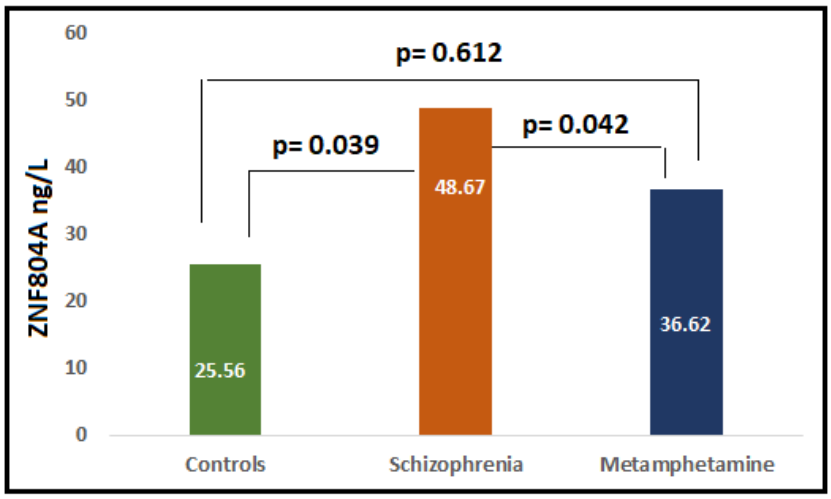

Fig. 1: Comparison of Zinc Finger Protein-804A (ZNF804A) level among control group, schizophrenia group and methamphetamine group.

Patients in schizophrenia group displayed higher level of this protein (48.67 ng/L, range=17.53-118.4 ng/L) than either controls (25.56 ng//L, range= 2.76-252.81 ng/L) or patients in methamphetamine group (35.62 ng/L, range=7.25-188.09 ng/L) with highly significant differences.

Molecular assays

The frequency of different genotypes in all the included study groups did not deviate significantly from Hardy Weinberg equilibrium.

The distribution of Genotypes and alleles of rs1344706 (ZNF-804A) polymorphism in schizophrenia patients and controls

The homozygous wild type of genotype (CC) was more frequent in controls (42%) than patients with schizophrenia (24%) with a significant difference. In contrast, the homozygous mutant genotype (AA) was more comoon in patients than controls (36% vs. 16%) (OR= 1.32, 95%CI= 1.32-11.75, p=0.014). This SNP seems to have recessive inheritance as the AA+AC genotypes were more common in patients with schizophrenia than controls (76% vs. 58%) although the difference exceeded the acceptable limit of significance. At allelic level, the mutant allele (A) was more frequent in patients than controls (56% vs. 37%) (OR=2.26, 95%CI= 1.28- 4.0, p= 0.005) as shown in Table 2.

The distribution of Genotypes and alleles of rs1344706 (ZNF-804A) polymorphism in methamphetamine addiction patients and controls

Although the AA genotype was more common in controls than patients (16% vs. 4%), the difference was not significant. Likewise, allele A was more frequent among patients with methamphetamine addiction (70%) than controls (63%) with no significant difference (Table 3).

The distribution of Genotypes and alleles of rs1344706 (ZNF-804A) polymorphism methamphetamine addiction and schizophrenia patients

A substantial variation in this distribution was found between methamphetamine addiction and schizophrenia patients. Both wild type and heterozygous genotypes (CC and AC) were far more frequent among patients with methamphetamine addiction (44% and 52%, respectively) compared with schizophrenia patients (24% and 40%, respectively) with highly significant differences.

In contrast, the homozygous mutant genotype (AA) was far more frequent among patients with

schizophrenia than those with methamphetamine addiction (36% vs. 4%) (OR= 11.7, 95%CI=02.43-56.4, p=0.002). Interestingly, the SNP demonstrated a significant variation between these two groups in both dominant and recessive models.

As indicated in Table 4, the mutant allele (A) was more common in individuals with schizophrenia than in those with methamphetamine addiction (56% vs. 30%), (OR= 2.74, 95% CI-=1.53-4.9, p= 0.001).

Table 2: SNP rs1344706 genotypes and alleles prevalent in schizophrenia patients and healthy controls

rs1344706	**Controls (n=50)**	**Schizophrenia (n=50)**	***P*-value**	**OR(95% CI)**
Genotypes				
CC	21(42%)	12(24%)	**0.048**	1.0
AC	21(42%)	20(40%)	0.285	1.67(0.65-4.25)
AA	8(16%)	18(36%)	**0.014**	**1.32(1.32-11.75)**
HWE	0.483	0.183		
Dominant models				
CC+AC	42(84%)	32(64%)	0.109	1.0
AA	8(16%)	18(36%)		2.95(1.14- 7.65)
Recessive model				
CC	21(42%)	12(24%)	0.058	1.0
AC+AA	29(58%)	38(76%)		2.29(0.97-2.5.41)
Alleles				
C	63(63%)	44(44%)	**0.005**	1.0
A	37(37%)	56(56%)		2.26(1.28-4.0)

Table 3: SNP rs1344706 genotypes and alleles prevalent in methamphetamine addiction patients and healthy controls

rs1344706	**Controls (n=50)**	**Meth (n=50)**	***P*-value**	**OR(95%CI)**
Genotypes				
CC	21(42%)	22(44%)	0.165	1.0
AC	21(42%)	26(52%)	0.693	1.18(0.52-2.71)
AA	8(16%)	2(4%)	0.091	0.24(0.04-1.26)
HWE	0.483	0.092		
Dominant models				
CC+AC	42(84%)	48(96%)	0.063	1.0
AA	8(16%)	2(4%)		0.22(0.04-1.09)
Recessive model				
CC	21(42%)	22(44%)	0.840	1.0
AC+AA	29(58%)	28(56%)		0.92(0.42-2.03)
Alleles				
C	63(63%)	70(70%)	0.294	1.0
A	37(37%)	30(30%)		0.73(0.4-1.32)

Table 4: SNP rs1344706 genotypes and alleles prevalent in methamphetamine addiction and schizophrenia patients

r rs1344706	**Schizophrenia (n=50)**	**Meth (n=50)**	***P*-value**	**OR(95%CI)**
Genotypes				
CC	12(24%)	22(44%)	**0.003**	**1.0**
AC	20(40%)	26(52%)	**0.001**	**16.5(3.26-83.49)**
AA	18(36%)	2(4%)	**0.002**	**11.7(02.43-56.4)**
HWE	0.183	0.092		
Dominant models				
CC+AC	32(64%)	48(96%)	**0.001**	**1.0**
AA	18(36%)	2(4%)		**13.5(2.93-62.2)**
Recessive model				
CC	12(24%)	22(44%)		**1.0**
AC+AA	38(76%)	28(56%)	**0.037**	**2.5(1.06-5.86)**
Alleles				
C	44(44%)	70(70%)	**0.001**	**1.0**
A	56(56%)	30(30%)		**2.74(1.53-4.9)**

DISCUSSION

In the present study, there was no substantial variation in serum ZNF804A levels between the methamphetamine addiction group and the healthy control group. However, ZNF804A was much higher in the schizophrenia group than in the controls and methamphetamine addicts. Although most prior studies found a correlation between schizophrenia and ZNF804A expression, none of them looked at the serum level of this marker in relation to schizophrenia. As a result, our finding that schizophrenia is linked with a lower level of ZNF804A is novel finding and

emphasizes the relevance of this marker in the diagnosis and prognosis of the disease, aside from the potential use of this protein in treatment purposes.

According to emerging evidence, the rs1344706 polymorphism has been associated with schizophrenia by numerous research groups. Finding possible markers and understanding the importance of ZNF804A in the pathogenesis of schizophrenia could lead to new remedy approaches (8). As there have been few studies on this relationship, this study looked at schizophrenia patients and healthy controls from the Iraqi population to investigate if there was a link between SNP rs1344706 and the risk of schizophrenia. Our study demonstrated a substantial link between ZNF-804A (rs1344706) SNP genotypes, AA, AC and CC and risk of schizophrenia as well as between alleles A and C and risk of schizophrenia with genotype AA and allele A being the main risk factors. Our results are in line with similar studies by Chen *et al*. (9) who reported AA to be more frequent (31.4 % versus 25.9 %) and CC to be less frequent (18.6 % versus 24.3 %). According to Riley *et al.* (10), A allele was shown to be significantly associated with schizophrenia (65% versus 61%, with an OR of 1.20 (1.03 − 1.40) and is agreement with our findings.

In line with our observation, there are previous reports that are linked between susceptibility to schizophrenia and gene polymorphism in ZNF-804A (rs1344706) (11). In two previous Chinese studies, a similar association between schizophrenia and gene polymorphism in ZNF-804A (rs1344706) was reported (9,12). On the contrary several reports have also disputed such a link (13-15), involving Asian and Chinese populations, wherein demonstrations failed to support an association between schizophrenia risk and ZNF-804A (rs1344706) genes and alleles. However, Li *et al*. discovered that Asians and Europeans have considerable variances in ZNF804A (15). The disparity between Europeans and Han Chinese is likely due to genetic heterogeneity, which is frequently reported in genetic association analysis for complicated diseases caused by different demographic characteristics. Other population-related features, like food, culture, or environment where they live, could also contribute to the observed variation (16).

The overexpression of ZNF804A impacts the expression of multiple genes associated with schizophrenia (17). Recently, researchers have identified a short, conserved region in mammals downstream of rs1344706 that may serve as a cis-acting element for the ZNF804A gene, potentially playing a significant role in the development of schizophrenia (18). Typically, proteins containing zinc-finger domains function as modulators and act as transcription factors, engaging in various interactions with RNA and proteins. ZNF804A has been found to influence the expression of schizophrenia-related genes such as PDE4B, COMT, PRSS16, and DRD (17). The conserved DNA sequence surrounding rs1344706, which contains transcription factor-binding sites, could potentially interact with the zinc-finger protein Myt1L and the POU3F1/Oct-6 POU domain transcription factor, promoting the differentiation and proliferation of oligodendrocytes (19).

Our finding is in contradiction to the finding of Esmaeili *et al.*, (20) who revealed no correlation between rs1344706 and susceptibility to schizophrenia. Our study findings disagree also with the observations of several previous studies which reported no significant association between ZNF-804A (rs1344706) SNP genotypes and alleles and susceptibility to schizophrenia (14, 21, 22).

On the other hand, in our study, we failed to prove an association between gene and alleles of ZNF-804A (rs1344706) SNP and susceptibility to methamphetamine addiction; with the exception of genotype AA which appears to be protective against such an addiction. A literature search for the association of SNP rs1344706 susceptibility to methamphetamine addiction yielded no results. Hence, based on our current knowledge, our research is groundbreaking as it pioneers the establishment of genetic susceptibility between ZNF-804A (rs1344706) SNP and methamphetamine addiction. Among the four gene-wide association studies (GWAS) published, two investigations on methamphetamine showed no substantial genome-wide links (23) while, the other two looked at amphetamine (24) and cocaine (25), and both discovered a single genome-wide significant SNP link, but these findings are yet to be validated.

METH use can result in METH-induced psychosis, a condition that needs immediate medical attention. Although knowing the difference between METH-induced and primary psychosis is vital for understanding their clinical outcomes, there is no clear diagnostic approach based on their symptoms. The clinical similarities between schizophrenia and METH-induced psychosis, in addition to epidemiological evidence of a genetic risk shared by the two diseases, make it challenging to differentiate between the two illnesses (23). Hence, genotyping of ZNF-804A (rs1344706) SNP and the serum levels of this protein could be used as a marker for diagnosis and screening of schizophrenia and methamphetamine addiction patients.

CONCLUSION

Zinc Finger Protein-804A (ZNF804A) AA genotype and A allele is a risk factor for schizophrenia. Serum levels of the ZNF804A could confirm schizophrenia in young individuals with subtle clinical features.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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