RESEARCH ARTICLE

Association of Illegal Behavior with GST Isoforms Null Genotyping in Methamphetamine Abuse Cases

Abdulnaser Saud[1], Zahraa A A Zaid[2], Zahraa H A Alzahraa[3], Rathab A Ahmed[4*]

[1]*Department of Medical Engineering, Al-Hadi University College, Baghdad, Iraq.*
[2]*Department of Medical Engineering, Mazaya University College, Iraq.*
[3]*College of Pharmacy, National University of Science and Technology, Dhi Qar, Iraq.*
[4]*Department of Medical Laboratories Technology/ AL-Nisour University College, Baghdad, Iraq.*

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ABSTRACT

The present study aims to detect the association of illegal behavior with GST isoforms in methamphetamine abuse cases. The present study targeted two GST isoforms included, GSTT1 and GSTM1. The results found a strong association between GSTT1 null genotyping and meth addiction cases (*p* 0.0078) that were more frequent in cases (46.80%) than the control grou*p* (17.24%), non-significant relation was observed between GSTM1 and GSTM1 null genotyping ($p = 0.1122$). Also, non-significant changes in the genotyping GSTT1 null GSTM1 and GSTM1 null GSTT1, and the normal GSTM1+GSTT1 genotyping with null genotyping of both genes. The distribution of GST null genotyping according to sex found non-significant differences observed between male and females in all genotypes GSTT1 ($p = 0.1181$), GSTM1 ($p = 0.6525$), GSTT1 null GSTM1 and GSTM1 null GSTT1 ($p = 0.8226$), finally GSTT1+GSTM1 with null both genes was ($p = 0.158$).

The null GSTT1 was more frequent in cases without illegal behavior (60.86%) in non-significant differences ($p = 0.1125$). Null genotyping of GSTM1 more frequent in cases without illegal behavior (43.47%) but didn't observe in illegal behavior cases in significant differences ($p = 0.0143$). Non-significant difference was recorded ($p = 0.1935$) in companies between GSTT1+ GSTM1 null genotyping. Finally, the differences between GSTT1 and GSTM1 and null both genes weren't observed in cases with illegal behavior than in cases without illegal behavior that recorded in (25%) in significant differences ($p = 0.0231$). The results concluded that the null genotyping didn't associate with illegal behavior represented by agitation and agitation with antisocial behavior. Furthermore, there was a strong correlation between meth abuse and GSTT1 null genotyping.

Keywords: Association, Illegal behavior, GST isoforms, Methamphetamine abuse cases.

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INTRODUCTION

Interpersonal violence prevention is still a public health priority in different countries. The cost of violence is very high for law enforcement, premature death, disability, and medical care.[1,2] In substance abuse cases. Violent behavior and victimization are common,[3,4] and the substance abuse is contributed of some violent incidents.[5] Thus, control of violent behavior and victimization has been more important in the last years.[6,7] Evidence reports their efforts to develo*p* different strategies to reduce these behaviors.[8]

Due to the high prevalence of methamphetamine (MA) use in the world, there has been increasing awareness of the deleterious impacts to exposure to MA, and the biochemical processing explorations by which such impacts are mediated. The toxicity mechanisms of MA have been well studied and these effects are represented in different ways, like excitotoxicity (high level of glutamate release), dysfunction of mitochondria,[9] dysfunction of blood-brain barrier, inflammation and damage of DNA,[10] the oxidative stress is very promising to explain the harmful effect of meth abuse. Meth is one type of amphetamine molecule that triggers the blood–brain barrier crosses easily and enhances the central nervous system (CNS) by acting as a sympathomimetic drug.[11] The acting effect of Meth is elevated synaptic availability of dopamine and serotonin.[12] But chronic exposure lead to neurotoxicity and long-lasting damage to the dopaminergic axon terminals.[13] After meth uptake the dopamine increased by auto-oxidization to toxic molecules like hydroxyl radicals (OH·), hydrogen peroxide (H_2O_2), and superoxide radicals (O_2^{-}) that lead to damage of cell components, including proteins, lipids, RNA and DNA.[14]

**Author for Correspondence: rathababbass2000@gmail.com*

The current study aims to evaluate the role of an important antioxidant enzyme gene GST in methamphetamine abuse cases that suffered from illegal behavior.

MATERIALS AND METHODS

About 47 methamphetamine abuse cases that were classified with and without illegal behavior were attended to the Al-Sadiq hospital in Hilla city for medication. All cases were diagnosed by the specialist psychiatric physician prof Dr. Kareem Naser Hussain during 3 months (May-July). The illegal behavior in this cases were agitation and agitation with antisocial, after clinical diagnoses, data and blood samples were collected from each case with written consensus according to ethical approval of the Ministry of Environment and Health in Iraq. The exclusion criteria of the current study were cancer, all types of diabetes mellitus, hypertension, autoimmune disease, and smoking.

Blood samples were transferred to lab by EDTA tubes then DNA was extracted by FavorPrep™ blood genomic DNA extraction mini kit, the PCR programs and conditions were GSTM1 F 5'-GAA, CTC, CCT, GAA, AAG, CTA, AAG, C-3', R 5'-GTT, GGG, CTC, AAA, TAT, ACG, GTG,G -3' to produce 215 b*p* and GSTT1: F 5'-TTC, CTT, ACT, GGT, CCT, CAC, ATC, TC-3', R 5'-TCC, CAG, GTC, ACC, GGA, TCA, T-3' to produce 312 bp, at TM 59ºC for 40 seconds, products were visualized using 1%, 0.5X TBE buffer, 70 V, 20 mA, for 40 minutes and staining with ethidium bromide. The genotyping was detected by amplification products and null genotyping by absent the amplification products belong to the deletion in target sequences (Figure 1).

Statistical analysis: results were represented as percentages and the significance was determined using odd ratio CI 95% test at *p-value* < 0.05.

RESULTS AND DISCUSSION

Methamphetamine abuse cases have been recorded in high rates in different governorates of Iraq in recent years. The present study found that the mean of age was (26.87 ± 1.12) years of cases and (26.76 ± 0.808) years of control in non-significant differences (t = 0.077, *p* = 939). The percentage of females was lower than male (25.53 and 74.46%) respectively. After (2003) the drug trade was significantly increased and this led to big problems among populations. This was documented in different studies and workshops.[15,16] In another study Al-Hemiery *et al.* (2014)[15] proposed that the most commonly used substances are hashish, alcohol and prescription drugs. New drugs in Iraq include amphetamine-type substances, crystal methamphetamine, and the painkiller tramadol. Methamphetamine addiction is also observed in other countries.[17,18] The methamphetamine abuse by females also reported in other studies like Bach *et al.* (2020)[19] that recorded 35% of their study population was women, and also in the Lorvick *et al.* (2012)[20] study.

The present work deals with the GST null genotyping association with methamphetamine abuse cases and illegal behavior in these cases. Results found a strong association

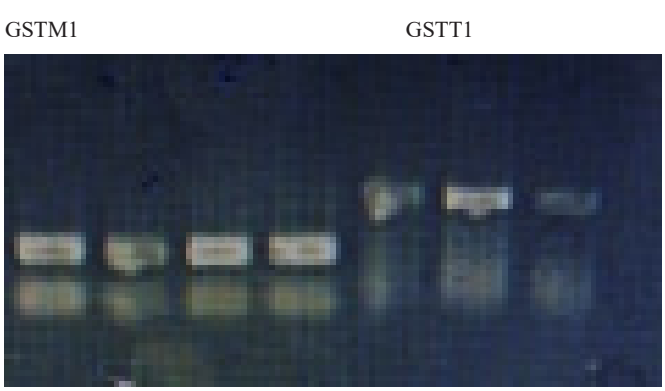

Figure 1: The GSTT1 and GSTM1 amplification products in 1% agarose gel

between GSTT1 null genotyping and meth addiction cases (OR = 4.5833, CI 95% 1.4939 to 14.0615, *p* = 0.0078) that more frequent in cases (46.80%) than the control grou*p* (17.24%). On the other hand, a non-significant relation was observed between GSTM1 and GSTM1 null genotyping (OR = 3.648, CI 0.7387 to 18.0215, *p* = 0.1122). Also non-significant changes in the genotyping GSTT1 null GSTM1 and GSTM1 null GSTT1 and the normal GSTT1 and GSTM1 genotyping with null genotyping of both genes (Table 1).

The distribution of GST null genotyping according to sex are clarified in Table 2, and non-significant differences observed between male and female in all genotypes GSTT1 (OR = 0.333 CI 0.0841 to 1.3219, *p* = 0.1181), GSTM1 (OR = 0.6750 CI 0.1220 to 3.7357, *p* = 0.6525), GSTT1 null GSTM1 and GSTM1 null GSTT1 (OR = 1.4762, CI 0.0491 to 44.4263, *p* = 0.8226), finally GSTT1+GSTM1 with null both genes was (OR = 5.0000, CI 0.5351 to 46.7204, *p* = 0.158).

The illegal behavior in the present study was represented by agitation and agitation with antisocial and its association with GST null genotyping. Results showed the illegal behavior didn't affect by GST genotyping. In Table 3, the null GSTT1 was more frequent in cases without illegal behavior (60.86%) in non-significant differences (OR = 0.3857, CI = 0.1189 to 1.2509, *p* = 0.1125). Null genotyping of GSTM1 was more frequent in cases without illegal behavior (43.47%) but didn't observe in illegal behavior cases in significant differences (OR = 0.0262, CI =0.0014 to 0.4835, *p* = 0.0143). The non-significant difference was recorded (OR = 7.9333, CI = 0.3497–179.9657, *p* = 0.1935) in companies GSTT1 and GSTM1 null genotyping, finally the differences between GSTT1 and GSTM1 and null both genes that didn't observe in cases with illegal behavior than in cases without illegal behavior that recorded in (25%) in significant differences between illegal behavior and these genes (OR = 33.0000, CI = 1.6164 to 673.7141, *p* = 0.0231) (Table 3).

As a result of meth addiction increasing in the wide world, health awareness is also growing about the harmful impacts of meth exposure. The meth toxicity mechanisms were well studied. The toxic effect appears in many ways like by releasing glutamate in excessive rate, causing mitochondrial dysfunction,[21] dysfunction of the blood-brain barrier, DNA damage and inflammation.[22] Some evidence have been found

Table 1: The GST genotyping distribution (GSTT1 and GSTM1) in study groups

GST genes	*Methamphetamine abuse cases (95%)*	*Control group (%)*	*Odd ratio (CI95%)*	*p-value*
GSTT1	25 (53.191%)	24 (82.75)	4.5833 (1.4939–14.0615)	0.0078
GSTT1 null genotyping	22 (46.80%)	5 (17.24)		
GSTM1	37 (78.72%)	27 (93.10)	3.6486 (0.7387–18.0215)	0.1122
GSTM1 null genotyping	10 (21.27%)	2 (6.89)		
GSTT1 null GSTM1	3 (6.38%)	2 (6.89%)	0.0750 (0.0096–0.5836)	0.0133
GSTM1 null GSTT1	16 (30.43%)	5 (17.24%)		
GSTT1+GSTM1	22 (46.80%)	22 (75.86%)	13.0000 (0.6905–244.7407)	0.0868
Non GSTT1 and GSTM1	6 (12.76%)	0		

Table 2: The GST genotyping distribution (GSTT1 and GSTM1) in methamphetamine abuse cases grou*p* according to sex

GST genes	*Female*	*Male*	*Odd ratio (CI95%)*	*p-value*
GSTT1	4 (33.33%)	21 (60%)	0.3333 (0.0841–1.3219)	0.1181
GSTT1 null genotyping	8 (66.66%)	14 (40%)		
GSTM1	10 (83.33%)	27 (77.14%)	0.6750 (0.1220–3.7357)	0.6525
GSTM1 null genotyping	2 (16.66%)	8 (22.85%		
GSTT1 null GSTM1	0 (0%)	3 (8.57%)	1.4762 (0.0491– 44.4263)	0.8226
GSTM1 null GSTT1	1 (8.33%)	15 (42.85%)		
GSTT1+GSTM1	2 (16.66%)	20 (57.2%)	5.0000 (0.5351–46.7204)	0.1581
Non GSTT1 and GSTM1	2 (16.66%)	4 (11.42%)		

the oxidative stress causes cellular level harmful impacts of MA abuse.

The association between illegal behavior and oxidative stress has been studied. Loo *et al*., (2021)[23] concluded that severe DNA destruction was strongly related to lifetime suicide attempts among lifetime suicidal ideators in bipolar disorder. A higher level of DNA damage was observed among cases of suicidal ideation in compared with the control group. A possible idea of the association between DNA damage by oxidative stress and illegal behavior is studied by Andreazza *et al.* (2007) and Raza *et al.* (2016)[24] that the major psychiatric disorders pathophysiology was caused by oxidative stress as well as the dysfunctional DNA repair to remove DNA lesions that lead to neurotransmission abnormality and weakness the neuroplasticity on to*p* of dysfunctional energy metabolism in the brain.[24] However, the causal association between suicidal behavior and DNA lesions still need a more in-depth longitudinal study for definitive conclusions.

In the present study, there was no correlation between GST genes null genotyping and illegal behavior represented by agitation and agitation with antisocial behavior. Low percentages of null genotyping was observed in meth case abuse with illegal behavior, the antioxidant mechanisms can explain this were varied in cells like antioxidants enzymes like catalase, superoxide dismutase, glutathione reductase and glutathione peroxidase.[25] These enzymes play vital role in removing ROS from body, thus further studies must be implemented to detect its role in the illegal behavior of meth

Table 3: The GST genotyping distribution (GSTT1 and GSTM1) in methamphetamine abuse cases grou*p* according to illegal behavior

GST genes	*Methamphetamine abuse cases without illegal behavior (%)*	*Methamphetamine abuse cases with illegal behavior (%)*	*Odd ratio (CI95%)*	*p-value*
GSTT1	9 (39.13%)	15 (66.66%)	0.3857 (0.1189–1.2509)	0.1125
GSTT1 null genotyping	14 (60.86%)	9 (33.33%)		
GSTM1	13 (56.52%)	24 (100%)	0.0262 (0.0014–0.4835)	0.0143
GSTM1 null genotyping	10 (43.47%)	0 (0%)		
GSTT1 null GSTM1	3 (13.04%)	0 (0%)	7.9333 (0.3497–179.9657)	0.1935
GSTM1 null GSTT1	7 (30.43%)	8 (33.33%)		
GSTT1+GSTM1	6 (25%)	16 (69.56%)	33.0000 (1.6164–673.7141)	0.0231
Non GSTT1 and GSTM1	6 (25%)	0 (0%)		

abuse cases. Also, other antioxidant molecules, like vitamins and minerals, contribute to the balance of ROS's toxic effect, which may be depleted in cases of illegal behavior.[26]

The earlier study found that the GST properties are mediated the thioether bond catalysis between GSH and electrophilic centers of small molecules.[27] The GSTs in humans are classified to double superfamilies, cytosolic and membrane-bound microsomal. The microsomal classes have three types encoded by one gene on chromosome 12 (*MGST1*), contributing on the endogenous of leukotrienes and prostaglandins metabolism.[28] A study deal with illegal behavior (suicide attempts) with catalase level found a negative association with the CAT level.[29,30] Some reports have found elevated SOD activity in patients with chronic schizophrenic,[31-34] while SOD activity has also been decreased in other reports.[35,36] Different illegal behaviors have been observed in Meth abuse cases that should be studied for further information.

CONCLUSION

Illegal behavior in meth abuse case is a complex health problem in addition to addiction. The present study concluded that the GST included (GSTT1 and GSTM1) isoforms null genotyping didn't associate with illegal behavior represented by agitation and agitation with antisocial. Furthermore, there was a strong association between meth abuse and GSTT1 null genotyping. Further investigations should be conducted to discover the association of illegal behavior with oxidative stress.

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