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Research Article

Association study between D_2 receptor A-241G, rs1799978 genetic variation and olanzapine efficacy in Iraqi schizophrenic patients

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Abstract

This study aimed to assess the role of D_2 receptor A-241G (rs1799978) genetic polymorphism and olanzapine response and safety in Iraqi schizophrenic patients. The case-control study composed of 100 schizophrenic patients consisting of both genders were recruited from the Psychiatry Outpatient Department and 50 apparently healthy volunteers, served as a control group. Patient response to olanzapine was evaluated with the aiding of the PANSS and genotyping of D_2 receptor A-241G (rs1799978) polymorphisms was detected using the nested PCR method. The heterozygous (AG) and mutant (GG) alleles of D_2 receptor A-241G (rs1799978) were significantly predominated in schizophrenic patients and absent in healthy volunteers. Schizophrenic patients with the G allele of D_2 receptor A-241G (rs1799978) and who were administered olanzapine exhibited a notable resistance to olanzapine. In conclusion, the genetic polymorphism of D_2 receptor A-241G (rs1799978) was significantly associated with resistance to olanzapine in Iraqi schizophrenic patients.

Keywords

Olanzapine, D_2 receptor, Schizophrenia, genetic polymorphism

Introduction

One percent of people worldwide suffer from schizophrenia, a serious mental condition, and 0.24 to 4.7% of persons in the Arab countries. Schizophrenia is the most prevalent psychiatric condition in Iraq, with prevalence increasing from 12% in 2000 to 15% in 2020 (Ahmed 2022). Effective antipsychotic medications primarily block dopamine (D_2) receptors, which is in line with the pathophysiology of schizophrenia (Carli et al. 2021). Atypical antipsychotic drugs are successful at treating both schizophrenia's positive and negative symptoms. They have proven effective in treating resistant forms of schizophrenia and have a lower risk of developing extrapyramidal symptoms (EPS) and other movement disorders, like parkinsonism, akathisia, dystonia, and tardive dyskinesia, which are linked to physical impairment and subjective discomfort and distress (Li et al. 2016). Olanzapine is an atypical antipsychotic drug that is frequently prescribed. It inhibits dopamine action at the post-synaptic receptor in the mesolimbic pathway, specifically at the D_2 receptors, by binding loosely to these receptors and readily dissociating, allowing normal dopamine neurotransmission to take place. As a result, it causes a decrease in the pleasant symptoms that patients experience, such as delusions, hallucinations, and slurred speech, cognition, and behavior (Grinchii and Dremencov 2020). Pharmacogenetic biomarkers seek to identify patients who may benefit from specific medications based

on genetic variations. This approach may allow for the improvement of antipsychotic agent treatment and multiple ineffective trials and the deterioration brought on by the lack of response could be avoided by early detection of patients who are resistant to treatment. In the treatment of psychiatric diseases other than schizophrenia, olanzapine has been widely used. Treatment-resistant psychoses typically require the physician to either change to a different monotherapy or add to the current strategy to increase the pharmacological profile without identifying the causes of resistance. As a result, patients are exposed to additional unfavorable side effects (Toto et al. 2019). Four studies on patients of Han-Chinese, Japanese, African American, and Thai descent reported conflicting results on the association between the A-241G (rs1799978) polymorphism and the risperidone response (Xing et al. 2007; Nuntamool et al. 2017). Investigations of the responsiveness to antipsychotic medication in Mexican patients with D_2 receptor A-241G genes for schizophrenia showed that patients with treatment resistance had a higher prevalence of the G allele (Escamilla et al. 2018). The aim of this study was to investigate the responsiveness of olanzapine and their associated with D_2 receptor A-241G (rs1799978) gene polymorphism in Iraqi schizophrenic patients.

Subjects, materials and methods

Subjects

The adult-aged patients or older of both genders were estimated for competence. Schizophrenic patients diagnosed based on the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) (Tandon et al. 2013). After completing a written consent form that contained a full explanation of the study's objective and a request to complete a specially created questionnaire, all participants were enrolled in the study. Patients were receiving 10 mg /day olanzapine from 6 months up to years with no additional disorder were included in this study. Patients with pervious hyperglycemia/diabetes, hypotension, weight gain, hyperprolactinemia, tardive dyskinesia before taking olanzapine or receiving treatment or any other medicine that interacts with olanzapine such as bromocriptine, levodopa, methyldopa were excluded from the study.

Study design

The case-control study was performed from December 2022 to Abril 2023 in Al-Hassan Al-Mojtaba hospital. The 100 patients consisting of both male and female, aged between 20 and 65 years were recruited from Psychiatry Outpatient Department and 50 apparently healthy without any disease comprising both males and females aged 20 to 63 years, were also enrolled, and served as a control group. The study was approved by the scientific and ethical committee, Kerbala University, college of pharmacy and Ministry of Health of Iraq- Karbala health department with the project being assigned No: 244.

Evaluation the patient response to olanzapine

The Positive and Negative Syndrome Scale (PANSS), which has three parts: Positive (P), Negative (N), and cognitive or General Psychopathology (G) was utilized by the psychiatrist to gauge the illness's severity and the patient's reaction to olanzapine. The General Psychopathology subscale has 16 items with a strong focus on cognition (G1–G16), while the Positive and Negative subscales each have seven items (P1–P7, N1–N7). This information is shown in Table 1. Each component is given a score between 1 and 7 according to severity, with 1 denoting absence, 2; minimum, 3; mild, 4; moderate, 5; moderate-severity, 6; severity, and 7; extremeness. A thorough definition and exact standards for each of the seven rating points are provided for each item on the PANSS. The minimum scores required by this scoring approach are 7 points for each of the Positive and Negative subscales and the cognitive symptoms had 16 points, for a total of at least 30 points. Positive, Negative, and Cognition each have maximum scores of 49, 49, and 112 points, respectively, for a combined maximum score of 210 points (Shankar and Nate 2007).

Table 1. Positive and negative syndrome scale (PANSS).

Positive (P)		Negative (N)		Cognitive psychopathology (G)	
P1	Delusions	**N1**	Blunted affect	**G1**	Somatic concern
P2	Conceptual disorganization	**N2**	Emotional withdrawal	**G2**	Anxiety
P3	Hallucinatory behavior	**N3**	Poor rapport	**G3**	Guilt feelings
P4	Excitement	**N4**	passive/apathetic social withdrawal	**G4**	Tension
P5	Grandiosity	**N5**	Difficulty in abstract thinking	**G5**	Mannerism and posturing
P6	Suspiciousness/ persecution	**N6**	Lack of spontaneity and flow of conversation	**G6**	Depression
P7	Hostility	**N7**	Stereotyped thinking	**G7**	Motor retardation
				G8	Uncooperativeness
				G9	Unusual thought content
				G10	Disorientation
				G11	Poor attention
				G12	lack of judgment and insight
				G13	Disturbing of volition
				G14	Poor impulse control
				G15	Preoccupation
				G16	Active social avoidance

Positive syndrome is characterized by symptoms like hallucinations, delusions, and disorganized thought. Cognitive, affective, and social deficiencies, such as deflection of emotion and passive disinterest, are characteristics of the negative syndrome. Many cognitive problems, including confusion, inadequate attention, inability to understand, and purposeful avoiding of people, make up general psychopathology.

Genotyping for D_2 receptor A-241G (rs1799978) polymorphisms detection

The genomic DNA was purified from 2 ml whole blood taken from schizophrenic patients and healthy volunteers using the phenol/chloroform method. According to a pervious study, the genotyping for D_2 receptor A-241G (rs1799978) polymorphisms was detected using the a two-step nested polymerase chain reaction (PCR) (Zahari et al. 2011). The procedure used an overall volume of 25.0 L, contained 200 ng of DNA template, 1.0 mM MgCl2, 0.2 mM dNTPs (Promega, Madison, Wisconsin, USA), 0.5 U of Biotool DNA Taq Polymerase (B&M Labs, Madrid, Spain), and 1 Biotool PCR buffer (B&M Labs, Madrid, Spain), and produced equal amplification of all alleles. The concentrations of the best primer (Invitrogen, California, USA) were discovered to be 0.15 to 0.40 M. Standard 0.2 mL Eppendorf PCR tubes were used for all PCRs, which were then run through an Eppendorf Mastercycler Gradient Cycler (Eppendorf, Hamburg, Germany). The initial PCR amplified a section of DRD2 from exons 3 to 4. Prior to the cycling program, at first, The DNA was denatured for two minutes at 94 °C. Thereafter, a total of 35 cycles of DNA annealing at 65 °C for one minute, extension at 72 °C for two minutes, and a final extension session at 72 °C for five minutes were carried out. To examine the PCR data, a 2.0% agarose gel (LE, analytical grade; Promega, Madison, Wisconsin, USA) stained in ethidium bromide in a 1 Tris-borate-EDTA (TBE) buffer was utilized. This process took 90 minutes at 130 V. The first PCR, which employed the primer sets, produced 276 bp-sized fragments. After the first PCR was successful, 2.0 L of the diluted PCR output was utilized as a template for a second PCR to identify wild-type or mutant alleles. The reaction mixture used for the second PCR was the same as the one used for the first. The second PCR consisted of 15 cycles with DNA being denaturized for 1 minute at 94 °C, annealed for 1 minute at 63 °C, and extended for 2 minutes at 72 °C. Following that, a 2.0% agarose gel and 1 TBE were used to analyze 10 mL of the second PCR result for 90 minutes at 130 V. The predicted fragment size of the products is 252 bp. The PCR primers sequence used for detection of the D_2 receptor gene A-241G (rs 1799978) were illustrated in Table 2.

Table 2. Primer sequence of D2 receptor A-241G (rs 1799978).

Primer	Sequence	Product Size (bp)
(A-241G rs 1799978)	Forward1 5- ACTGGCGAGCAGACGGTGA -3	252 bp
	Reverse1 5- TGAAGCTGGACAGCTCTGC -3	
	Forwad2 5- CAGCCTGCAATCACAGCTTA -3	
	Reverse2 5- CAGCCTGCAATCACAGCTTG-3	

Statistical analysis

Statistical analysis will be performed using Statistical Package for Social Sciences (SPSS 26). Descriptive statistics for the numerical data were present as the mean and standard error of the mean (Mean ± SEM) and the non-numerical data were number and %. The normal distribution of data was tested with the aid of Shapiro – Wilk test. Numerical data will be analyzed by using an independent sample T-test and a one-way ANOVA-post-hoc-LSD test. Non-numerical data will be analyzed by using the Chi-square test. The multinomial logistic regression was used to assess the association of genetic variation with efficacy of olanzapine. The P values less than 0.05 will be considered statistically significant.

Results

Demographic data

The demographic data including age, gender, and BMI were assessed in both healthy and schizophrenia volunteers. In terms of age and gender, there were no real distinctions ($P > 0.05$) between the healthy volunteers and those with schizophrenia as show in Table 3. Schizophrenic patients demonstrated significant weight gain, as evidenced by increased BMI 29.11 ± 0.64 in schizophrenic males and 30.01 ± 0.81 in schizophrenic females compared to the healthy individuals 24.52 ± 0.57 in males and 24.89 ± 0.69 in females ($P < 0.05$) as shown in Table 3.

Table 3. Demographic data of both healthy and schizophrenic volunteers (data present as mean ± S.E and No (%)).

Variables		Volunteer		*P* – value
		Healthy (n = 50)	Schizophrenic (n = 100)	
Age (y)		38.98 ± 1.73	39.11 ± 1.44	0.256
Gender	Male	32 (64%)	18 (36%)	0.190
	Female	55 (55%)	45 (45%)	
BMI (kg/m^2)	Male	24.52 ± 0.57	29.11 ± 0.64	<0.0001*
	Female	24.89 ± 0.69	30.01 ± 0.81	<0.0001*

*: Significant effect ($P < 0.05$) compared to healthy group.

Prevalence of D_2 receptor genes A-241G (rs1799978)

The results of genotype D_2 receptor A-241G (rs1799978) genetic polymorphism showed a clear band with a molecular size 252 bps as presented in Fig. 1. The wild allele (AA) was predominated (100%) in healthy volunteers and about (78%) in schizophrenic patient, while the heterozygous type (AG) and mutant type (GG) were only presented in schizophrenic individuals with ratio of 14% and 8% respectively as shown in Fig. 2. The frequencies of the D_2 receptor alleles rs1799978 (A-241G) were significantly different between the healthy and schizophrenic volunteers ($P < 0.05$) as show in Table 4. There were significantly difference among male gender of healthy and schizophrenic individuals and There were no significantly difference among female gender of healthy and schizophrenic individuals regarding three different alleles of rs1799978 (A-241G) ($P > 0.05$) as explained in Tables 5, 6 and Fig. 3.

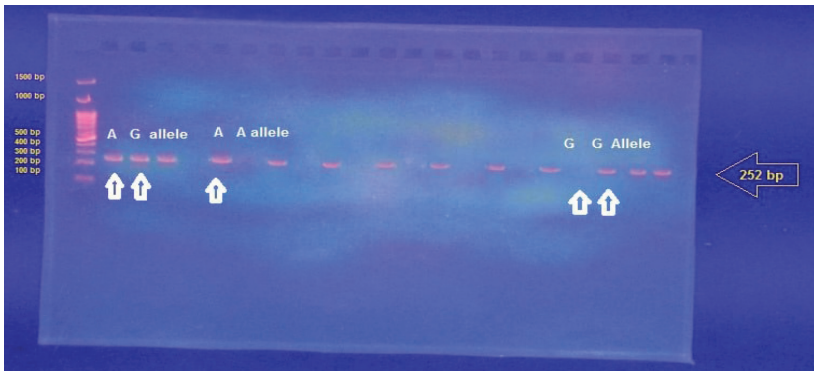

Figure 1. Genotyping of D_2 receptor genes A-241G (rs1799978).

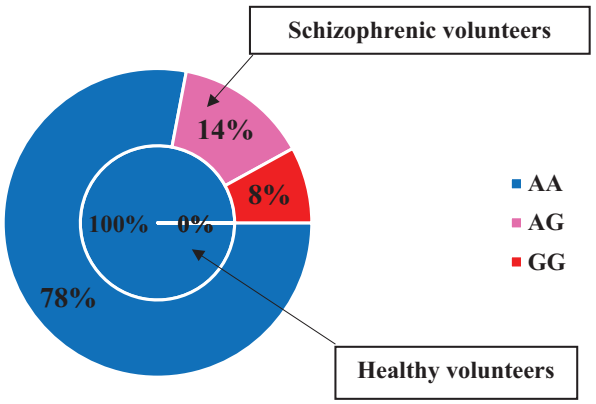

Figure 2. The Prevalence of D_2 receptor alleles A-241G (rs1799978) among volunteers.

Table 4. The Prevalence of D_2 receptor alleles A-241G (rs1799978) among volunteers (data present as No (%)).

Volunteers	Alleles of rs1799978 (A-241G)			*P* – Value
	AA	AG	GG	
Healthy	50 (100%)	0 (0%)	0 (0%)	0.002*
Schizophrenic	78 (75%)	14 (14%)	8 (8%)	

*: Significant effect (P < 0.05) between all groups.

Effects of D_2 receptor alleles A-241G (rs1799978) on PANSS

The schizophrenic symptoms were represented by PANSS score which was significantly high in schizophrenic patients who taken olanzapine and had either heterozygous (AG) allele 146.93 ± 4.91 or mutant (GG) allele 197.13 ± 4.07 of A-241G (rs1799978) as compared to those with wild (AA) allele 70.54 ± 2.46 ($P < 0.05$) as shown in Table 7. There were significantly difference among schizophrenic volunteers who carried heterozygous (AG) allele and mutant (GG) allele of A-241G (rs1799978) regarding the PANSS score ($P < 0.05$) as shown in Table 7 and Fig. 4. There were significantly associated between response of schizophrenic patient according to PANSS and G allele of A-241G (rs1799978) (95% CI = 7.098, 9.067) for patients carry heterozygous (AG) allele and (95% CI = 7.006, 9.237) for patients carry mutant (GG) allele ($P < 0.05$) as explained in Table 8.

Table 5. The Prevalence of D_2 receptor alleles A-241G (rs1799978) among male volunteers (data present as No (%)).

Male volunteers	Alleles of rs1799978 (A-241G)			*P* – Value
	AA	AG	GG	
Healthy	32 (100%)	0 (0%)	0 (0%)	0.037*
Schizophrenic	45 (81.8%)	4 (7.3%)	6 (10.9%)	

*: Significant effect (P < 0.05) between all groups.

Table 6. The Prevalence of D_2 Receptor alleles A-241G (rs1799978) among female volunteers (data present as No (%)).

Female volunteers	Alleles of rs1799978 (A-241G)			*P* – Value
	AA	AG	GG	
Healthy	18 (100%)	0 (0%)	0 (0%)	0.052
Schizophrenic	33 (73.4%)	10 (22.2%)	2 (4.4%)	

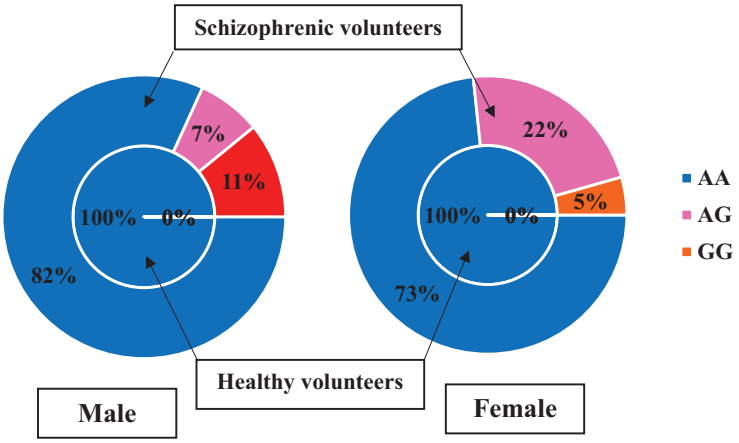

Figure 3. The Prevalence of D_2 receptor alleles A-241G (rs1799978) among both male and female volunteers.

Table 7. The PANSS score of schizophrenic and healthy volunteers (data present as mean ± S.E).

Variables	Volunteer				*P* -value
	Healthy	Schizophrenic			
		AA	AG	GG	
PANSS	30.24 ± 0.32	70.54 ± 2.46	146.93 ± 4.91	197.13 ± 4.07	<0.0001*

a: Significant effect (P < 0.05) among all study groups.

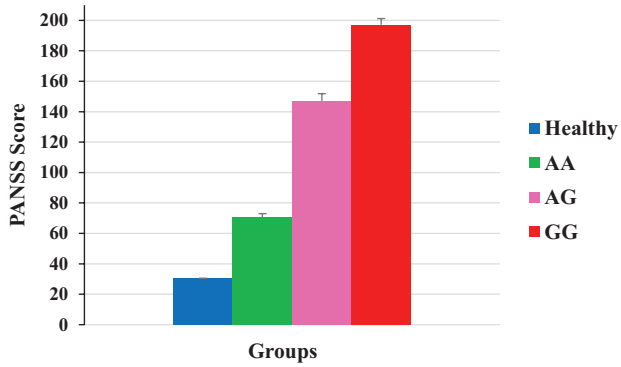

Figure 4. The PANSS score of schizophrenic and healthy volunteers.

Table 8. The multinomial logistic regression of D_2 receptor alleles A-241G (rs1799978) and PANSS score.

Variable	Allele of A-241G	OR (95% CI)	*P* -value
PANSS	AA	1*	
	AG	8.022 (7.098–9.067)	<0.0001a
	GG	7.928 (7.006–9.237)	<0.0001a

a: significant effect (p < 0.05), OR: Odds Ratio, CI: Confidence interval, *: reference group.

Discussion

Although olanzapine is the most widely used atypical antipsychotic medication, it is also used to treat a variety of disorders including autism, schizophrenia, bipolar disorder, and anorexia nervosa. Its resistance, which was brought on by some psychiatric disorders such the negative symptoms of schizophrenia, may cause restrictions on use or the need to switch to another antipsychotic drug or add antidepressants, both of which may exacerbate unpleasant side effects (Leucht et al. 2009; Lang et al. 2023). Another clinical trial found that olanzapine did not improve the positive and negative symptoms in some patients with refractory schizophrenia after failure of typical or atypical antipsychotic agents (Lindenmayer et al. 2002). The exact mechanism of schizophrenia developed resistance to olanzapine remains unknown.

This study explained the present heterozygous (AG) and mutant (GG) alleles of D_2 receptor alleles A-241G (rs1799978) among both gender of Iraqi schizophrenic patients and not presented in healthy volunteers. The similar outcome was shown in Thai children and adolescents with autism, and this genetic variant displayed non-stable clinical symptom (Nuntamool et al. 2017). A Canadian study found that aggressive kids were more likely to have two copies of the G gene at A-241G (Zai et al. 2012). Another investigation found that the D_2 receptor allele A-241G (rs1799978) gene is encodes a high level of D_2 receptor, which may result in inadequate risperidone blocking of these receptors and unstable clinical symptoms (Arinami et al. 1997).

In this study, the schizophrenic symptoms according PANSS score in patients with either heterozygous (AG) and mutant (GG) alleles of D_2 receptor alleles A-241G (rs1799978) and taken olanzapine were not significantly improved in comparison to those with wild (AA) allele Numerous clinical research found that in the Han Chinese and Japanese populations, carriers of the AA allele of A-241G had greater PANSS score improvements and responses to antipsychotic medications than carriers of the AG and GG alleles (Ma et al. 2019). In relation to SNP A-241G, Ikeda et al. found relationships between the A allele and response and the G allele and absence of response (Ikeda et al. 2008). Another study found that a high dopamine concentration at the mesolimbic loop is linked to rapidly developing positive symptoms; as a result, people with the G allele of A-241G experience psychiatric symptoms, have poor responses to many antipsychotic medications, and need high doses of one or a combination of antipsychotic agents (Yamanaka et al. 2016). In contrast, a different study discovered that the D_2 receptor allele A-241G (rs1799978) genetic polymorphism was substantially related with olanzapine sensitivity, and G allele carriers demonstrated greater response to olanzapine compared to patients with wild AA (Yan et al. 2020).

Conclusion

In conclusion, the genetic polymorphism of D_2 receptor A-241G (rs1799978) was significantly associated with resistance to olanzapine in Iraqi schizophrenic patient.

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Zahra Jawd Mohammed Ali: Conducted all experimental and analytical work and wrote the manuscript.; Atheer Majid Rashid Al-juhiashi: Provided supervision throughout the project and proofread the manuscript.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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