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Association of Serotonin 1 A Receptor(5-HT1A) (rs6296G/C) Gene Polymorphism and Serotonin Levels in Patients with Psychological Stress

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العلاقة بين التغاير الوراثي لمستقبل السيروتونين (5-HT1A)في القطعة الجينية rs6296G/C ومستويات السيروتونين في مرضى الاجهاد النفسي

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ABSTRACT:

Background: Stress has been linked to a number of psychological conditions, including major depressive disorder, schizophrenia, and Alzheimer's disease (AD). Serum serotonin levels and serotonin receptor gene polymorphism were thought to be linked to psychological stress-related illness symptoms.

Materials and Methods: In this study, 60 male patients with psychological stress were divided into 20 groups: those with Alzheimer's, schizophrenia, and major depression. Thirty-nine individuals were included as a healthy group. Serum serotonin levels were measured by ELISA, and the results were correlated with the serotonin 1 A receptor (5-HT1A) (rs6296G/C) gene polymorphism.

Results: The findings indicated a statistically significant ($p \leq 0.05$) reduction in serotonin levels across all patient groups when compared to the healthy group. Additionally, the serotonin receptor (rs6296G/C) gene polymorphism results demonstrated that the majority of patients with Alzheimer's and schizophrenia had the highest percentage (50%) of 5-HT1A genotype GC when compared to the healthy group.

Conclusion: It was determined that serotonin levels and 5-HT1A gene polymorphism are related in psychological stress disorders, such as depression, schizophrenia, and Alzheimer's disease.

Keywords: Stress; major depression; schizophrenia; Alzheimer's disease; serotonin levels, and polymorphisms in the serotonin receptor gene.

INTRODUCTION

In today's world, stress is inevitable, and a plethora of research has demonstrated the detrimental effects of psychological stress on immune function [1]. Stress has been linked to a number of psychological illnesses, including Alzheimer's disease (AD), a degenerative neurological condition that causes memory loss, learning disabilities, and significant alterations in behavior and personality [2]. AD is an age-related condition that affects 10% of people between the ages of 65 and 75 and roughly 32% of those over the age of 80, though few cases have been found in younger people [3]. AD is connected with a considerable load on caregivers and the healthcare system because people with AD have higher medical demands and expenses related to their care [4]. It has been found that AD patients have lower brain concentrations of serotonin and 5-HIAA [5]. Schizophrenia is another disorder linked to psychological stress. It is characterized by negative symptoms like low motivation and expressiveness, as well as cognitive deficits like poor executive functions, memory, and mental processing speed, as well as psychotic symptoms like delusions, hallucinations, and disorganized speech [6]. Roughly 1% of people worldwide suffer from schizophrenia, which is among the top ten causes of disability globally. On the other hand, individuals with schizophrenia exhibit a wide range of abilities in daily life; some are profoundly disabled, while others are able to function at a high level [7]. The promoter polymorphism of the 5-HT1A receptor gene (rs6295, C-1019G) has been linked to the impact of treatment on negative symptoms in individuals with schizophrenia [8]. Furthermore, psychological stress is linked to major depression disease (MDD), which is a global concern and the leading cause of burden and impairment globally [9]. Most serotonin receptor classes have been implicated in the development of anxiety and/or depression [10–11]. For example, 5-HT1A has been extensively linked to the pathophysiology of anxiety and depression [11]. Alterations in the serotonergic and kynuramine routes of tryptophan metabolism are associated with the pathogenesis of Alzheimer's disease. For instance, [12] shows that elevated tryptophan breakdown via the kynuramine pathway may be responsible for the low plasma tryptophan levels in AD. Furthermore, individuals with minor to moderate AD or healthy volunteers exhibiting tryptophan deficiency demonstrated alterations in cognitive function. Deficiencies in serotonergic transmission, characterized by a reduction in serotonin levels (5-hydroxytryptamine, 5-HT) the neurons and their projections, along with increased 5-HT autoinhibition, have been linked to major depressive disorder and inadequate antidepressant response in both preclinical and clinical research [13]. The present investigation aimed to ascertain the serotonin levels in people and the correlation between 5-HT1A gene polymorphism and serotonin levels in patients experiencing psychological stress compared to healthy groups.

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MATERIALS & METHODS

1. Study groups and collection blood samples

Ninety male subjects, ages 19 to 92, participated in the current study. The study population was split up into four groups: thirty patients made up the healthy group; thirty patients each from the three patient groups comprised 60 patients with psychological stress, divided into 20 patients each for major depression, schizophrenia, and AD. Using a disposable syringe, five milliliters of blood were drawn from both the patient and healthy groups. The blood was then transferred to a plain tube and allowed to clot for fifteen minutes at room temperature (20–25°C). Following a 15-minute centrifugation at 3000 rpm on the clotted blood, the serum was extracted and divided into 0.25 ml aliquots in Eppendorf tubes for physiological testing. For genetic testing, three milliliters of blood were venipunctured using a disposable syringe (5 milliliters) and put in an EDTA tube[14].

2.Estimation the level of serum serotonin

The human enzyme-linked immunosorbent assay kit (Sunlong, China) was utilized to measure the amount of the physiological parameter serotonin in serum using an ELISA Reader and washer (Biotek, USA).

The essential assay: Various antigen-antibody combinations are employed in ELISA, and colorimetric assessment of enzyme activity is consistently conducted using an enzyme-conjugated antigen or antibody. A substrate altered by the enzyme, resulting in a color change, is employed to evaluate enzyme activity. Following the incorporation of the substrate, the product's absorption of light is measured and expressed in numerical values. An ELISA is the term used to describe the assay, depending on the antigen-antibody combination.

3.MOLECULAR STUDY

A. DNA extraction

Using a DNA extraction kit, genomic DNA was extracted from whole blood samples from 90 patients and 30 seemingly healthy controls.

B. Primers selection:

The 5-HT1A gene polymorphism (rs6296G/C) was detected using PCR primers that were based on references [15].The source of these primers was (OligoTM/Korea). as displayed in table (1).

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Table (1): Primers of 5-HT1A receptor (rs6296G/C)

(5-HT1A) (rs6296**G/C)**	**Sequences (5'….3')**	**Tm/°C**	**Product size**
anti-sense primer	5-TGT TCC TAC ACT CCA GGC ACT GTT C-3	60.4	205bp
Sense primer G	5-GGA GAC TCG CAC TTT GAC TTG GTT G-3	59 .9	
Sense primer C	5-GGA GAC TCG CAC TTT GAC TTG GTT C-3	60.4	
anti-sense primer	5-TGT TCC TAC ACT CCA GGC ACT GTT C-3	60.4	342 bp
Sense primer sequencing	5- TTG CAG ATA GGC ATC ACT AGG GAG-3	58.1	

C. PCR detection of 5-HT1A(rs6296G/C)

The PCR reaction was carried out with a 20 µl total volume. The PCR master mix was made using Bio Master Mix (Korea), which performed two reactions for every sample in compliance with the manufacturer's instructions (Tables 2, 3).

Table(2): PCR components of 5-HT1A gene (rs6296)G Allele

PCR Master mix	**Volume**
Common reverse primer (10 pmol)	1 µl
G-allele forward primer (10 pmol)	1 µl
DNA template	4 µl
Free nuclease water	4 µl
master mix	10 µl
Total volume	20 µl

Table(3): PCR components of 5-HT1A gene (rs6296)C Allele

PCR Master mix	**Volume**
Common reverse primer (10 pmol)	1 µl
C-allele forward primer (10 pmol)	1 µl
DNA template	4 µl
Free nuclease water	4 µl
master mix	10 µl
Total volume	20 µl

The reaction blend was subjected to a thermal cycler manufactured by Cleaver Scientific, UK. The 5-HT1A gene was identified by PCR amplification under the following conditions, which are listed in table (4) and reported in the reference.

D. PCR Thermo cycler conditions:

Table (4): Program used for 5-HT1A receptor (rs6296) amplification.

PCR step	Temp.	Time	No of cycles
Initial denaturation	95^{O}C	5 min.	1
Denaturation	95^{O}C	30sec.	35
Annealing	60^{O}C	35sec.	
Extension	72^{O}C	1min.	
Final extension	72^{O}C	5 min	1
Hold	4 ^{O}C	Forever	-

E. PCR Product Electrophoresis:

The PCR product was run through a 1% agarose gel electrophoresis. The first well of the gel was filled with six microliters of the ladder DNA (100 bp), and each well was filled with five microliters of the PCR sample. After closing the electrophoresis tank lid, 30 minutes of 60 volt power was applied.

4. STATISTICAL ANALYSIS

ANOVA data analysis was conducted utilizing IBM SPSS Program version 20, with a post hoc test employed to determine significant differences between means [16]. The data were presented as mean, and a one-way ANOVA analysis of variance was conducted. Data were presented as odds ratios, and the Chi-squared (χ^2) test, applicable when the anticipated count is fewer than 5, was employed to evaluate the relationship between any two categorical variables [17].

RESULTS AND DISCUSSION

1. The level of serotonin:

Results presented in Table 5 indicate that serotonin hormone levels in each of the patient Groups exhibited significant differences lower ($p \leq 0.05$) than those in the healthy group. The hormone levels measured were 25.26 ± 2.68, 23.59 ± 1.79, and 22.74±1.69 (pg/ml) for patients with Alzheimer's, schizophrenia, and major depression, respectively, in contrast to 47.25±3.37 (pg/ml) in the healthy group. The findings of the current study indicated that serotonin levels hormone levels not significantly ($P \geq 0.05$) among the patient groups.

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Table (5): The levels of serotonin(5-HT) (means ± SE) in psychological stress patients and control groups.

parameter / Groups N=90	Serotonin (pg/ml)
Control group(30)	B 47.25±3.37
Alzheimer patients(20)	A 25.26±2.68
Schizophrenia patients(20)	A 23.59±1.79
Major depression patients(20)	A 22.74±1.69

Note: At (p≤0. 05), Different letters indicate a significant a difference.

Data from Table 5 indicated a substantial (p≤0.05) reduction in serotonin levels in individuals with AD relative to the healthy group. These findings align with a research [18] indicating that decreased serotonin levels in the brains of Alzheimer's patients can result in numbness, cognitive impairments, and accelerated aging. Furthermore, there is a notable (p≤0.05) reduction in serotonin levels in individuals with schizophrenia compare to the healthy group. These findings were incongruent with prior studies [19] that suggested at least a subset of schizophrenia patients have a pathogenic role for the serotonin system. Additionally, a study by [20] found that deficiency in 5-HT innervation related to development, long-term stress, or brain injury may cause depression. These findings were consistent with the significant (p≤0.05) decrease in serotonin hormone levels in major depression patients compared with the healthy group.

2.Genetic study

Table (6) and Figure (1) demonstrated that, when compared to patient groups, the healthy group had the highest percentage (76.67%) in 5-HT1A genotype GG. Similarly, when compared to other groups, the Alzheimer's and schizophrenia patient group had the highest percentage (50%) in 5-HT1A genotype GC, but the major depression patient group had the highest percentage, reaching 50% in 5-HT1A genotype CC. The data also revealed that, in comparison to other groups, the AHC group had the lowest percent of 5-HT1A genotype GC (6.67%), while the patient groups had a lower percent of 5-HT1A genotype GG (compared to the AHC group). Additionally, the current study's results demonstrated that the AHC group had the highest percentage of 5-HT1A allele G when compared to other groups, and the groups representing patients with major depression, schizophrenia, and AD had the highest percentage of 5-HT1A allele C when compared to the AHC group. In contrast to the AHC group, the patient groups displayed a lower percentage of 5-HT1A allele G. However, when compared to the healthy group (95% CI 2.52 to 34.58) P<0.05 $\chi 2$=12.5, the frequency of 5-HT1A receptor allele C was higher in Alzheimer disease, with an odds ratio of 9.33. Furthermore, compared to the group healthy, the frequency of 5-HT1A receptor allele C was higher in schizophrenia disease, with an odds ratio of 12.00 (95% CI 3.11 to 46.33). P<0.05 $\chi 2$= 14.90, however the frequency of 5-HT1A receptor allele C was greater in the group of individuals diagnosed with major depressive disorder, with an odds ratio of 7.43 (95% CI 2.06 to 26.78) than in the healthy (P<0.05 $\chi 2$= 10.31) group. Figures (2), (3), (4), (5), and (6) illustrate this.

Table (6) : Distribution and association of 5-HT1A receptor gene polymorphism with psychological stress patients and control groups.

parameters / groups	Genotype		Allele		χ2	P-value	OR	CI 95%
control group	GCn(%) CCn(%) GGn(%)	2(6.67) 5(16.67) 23(76.67)	Cn(%) Gn(%)	6(20) 24(80)	-	-	-	-
Alzheimer Patients	GCn(%) CCn(%) GGn(%)	10(50) 9(45) 1(5)	Cn(%) Gn(%)	14(70) 6(30)	12.5	0.00040	9.33	2.52 to 34.58
Schizophrenia patients	GCn(%) CCn(%) GGn(%)	10(50) 9(45) 1(5)	Cn(%) Gn(%)	15(75) 5(25)	14.90	0.00011	12.00	3.11 to 46.33
Major depression Patients	GCn(%) CCn(%) GGn(%)	6(30) 10(50) 4(20)	Cn(%) Gn(%)	13(65) 7(35)	10.31	0.0013	7.43	2.06 to 26.78

p-value ≤ 0.05 was significant

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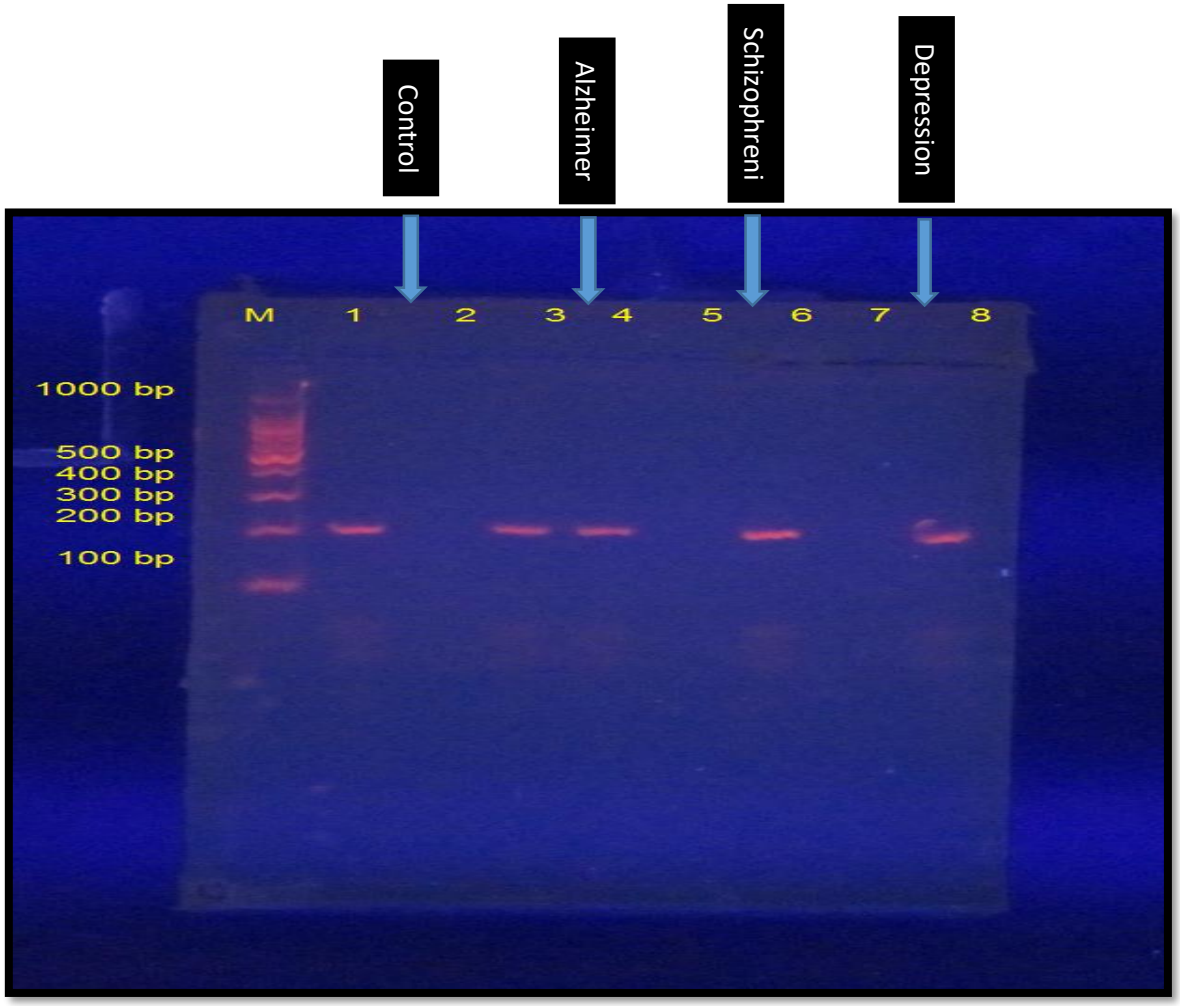

Figure (1) : The distribution and correlation of serotonin receptor (5-HT1A) gene polymorphism with psychological stress patients and AHC groups. The allele frequency for the control group was GG, for Alzheimer's disease patients it was GC, for schizophrenia patients it was CC, and for major depression patients it was CC.

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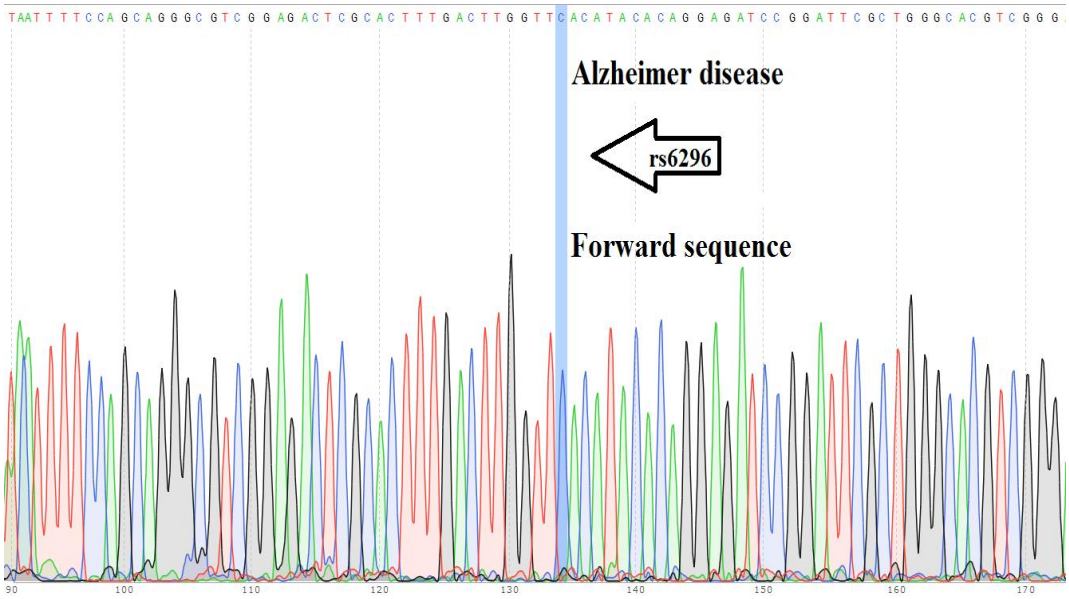

Figure (2): The distribution and correlation of the serotonin receptor gene polymorphism allele sequence revealed that the mutation allele C was the allele forward sequence associated with Alzheimer's disease.

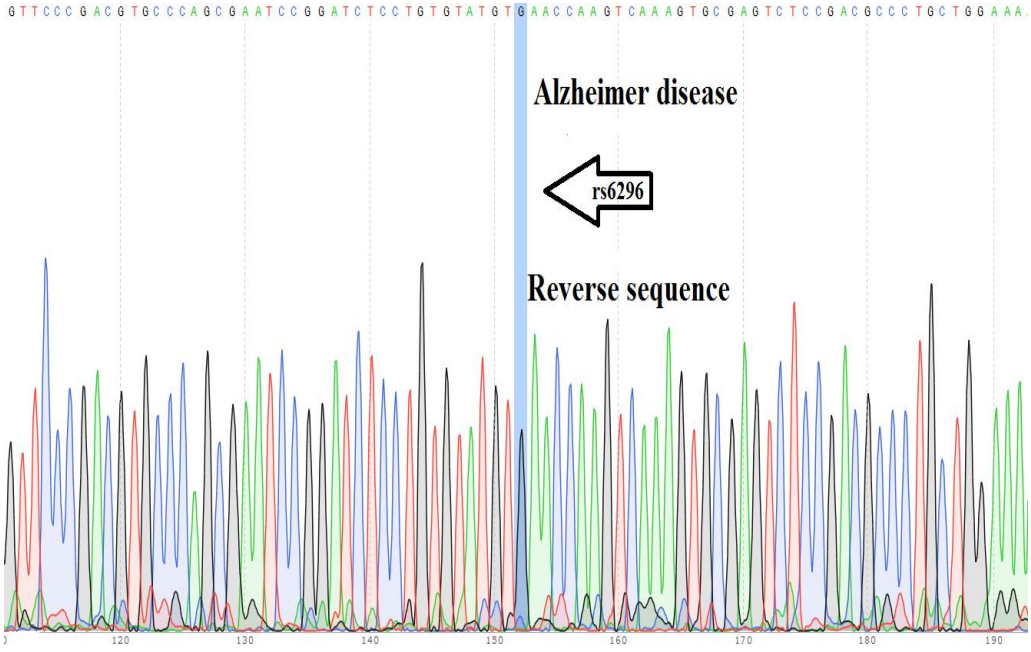

Figure (3): The distribution and correlation of the serotonin receptor gene polymorphism allele sequence revealed that the G (mutation allele) allele reverse sequence was associated with Alzheimer's disease.

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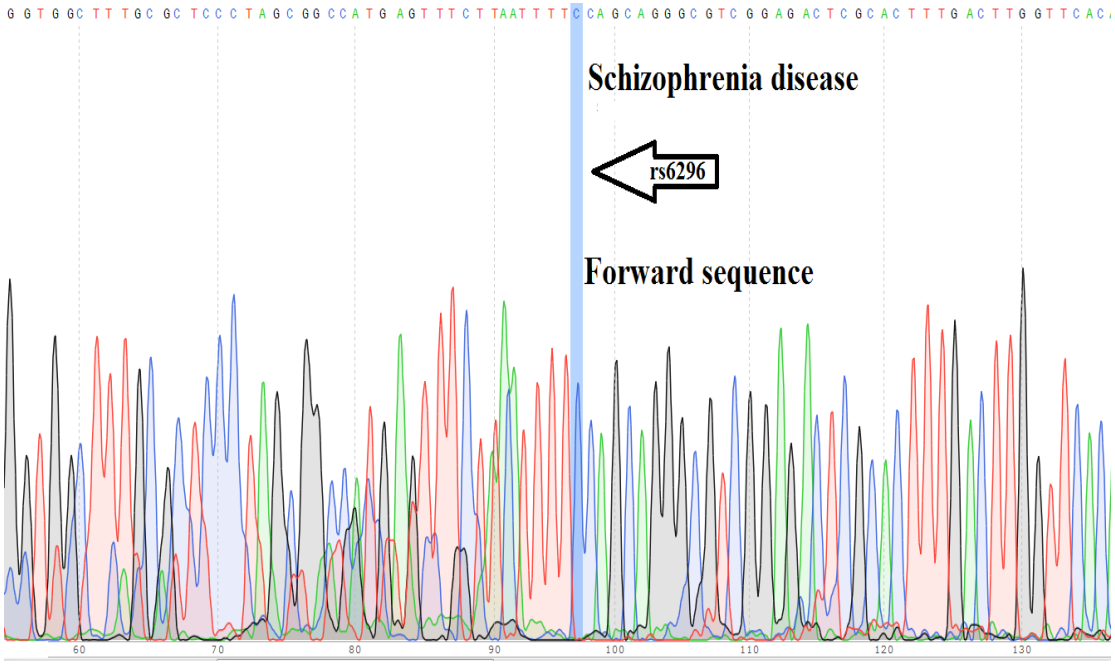

Figure (4): The distribution and correlation of the serotonin receptor gene polymorphism allele sequence revealed that the C mutation allele was the allele forward sequence associated with schizophrenia.

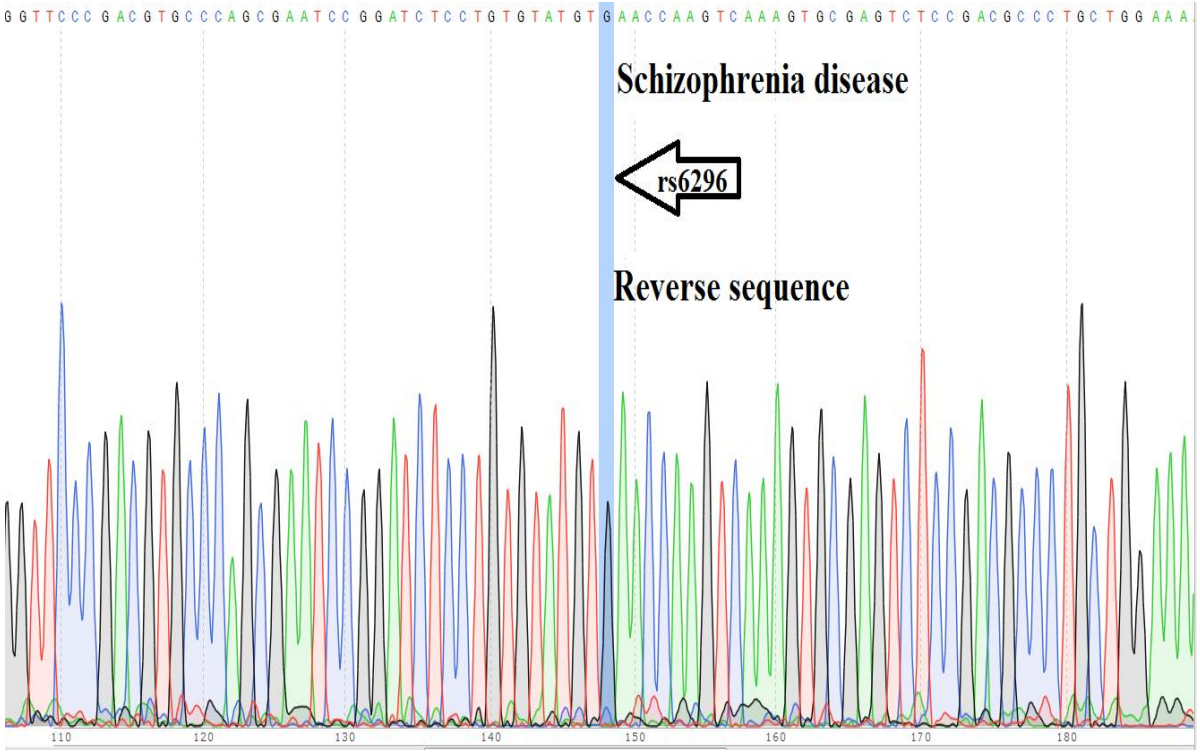

Figure (5): The distribution and correlation of the serotonin receptor gene polymorphism allele sequence revealed that the G (mutation allele) allele reverse sequence was associated with schizophrenia.

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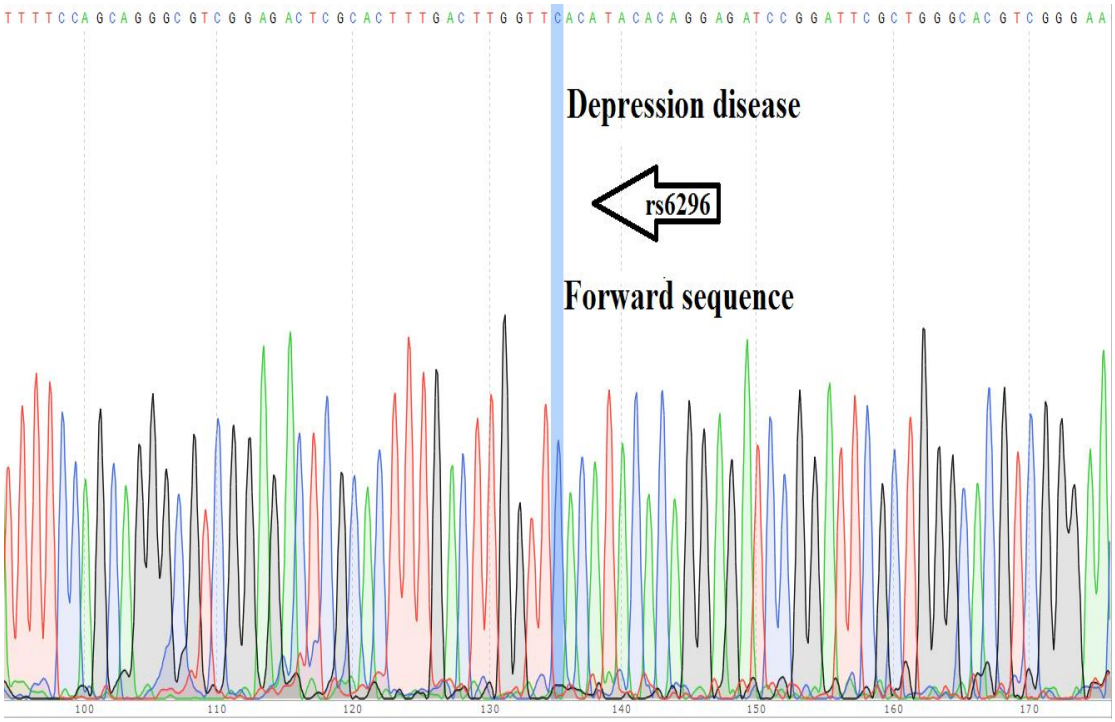

Figure (6): The distribution and correlation of the serotonin receptor gene polymorphism allele sequence revealed that the mutation allele C was the allele forward sequence associated with depression.

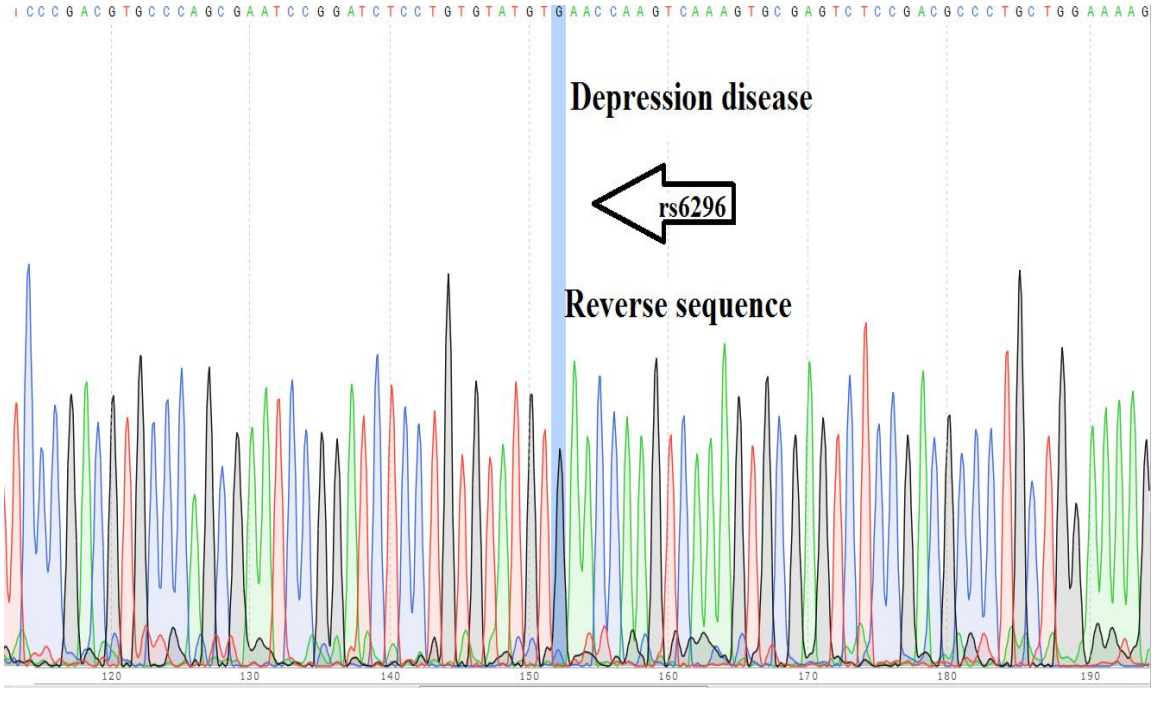

Figure (7): The distribution and correlation of the serotonin receptor gene polymorphism allele sequence revealed that the G (mutation allele) allele was the reverse sequence in depression.

In comparison to control groups, Table (6) revealed that the group of Alzheimer's patients had the highest percentage (50%) of 5-HT1A genotype GC. The findings align with a research [21] indicating that the 5-HT1A gene C (-1019)G variant may be associated with AD and that the (-1019)G allele might serve as a risk factor for AD. When compared to control groups, the 5-HT1A genotype CC percentage was highest in schizophrenia patient groups (65%). This finding was supported by research [22] which demonstrated that the G/C genotype is linked to higher 5-HTR1A density in presynaptic neurons in the raphehowever, a Chinese study21 found that patients with schizophrenia treated with risperidone showed a greater improvement in negative symptoms if they had a CC genotype of -1019C/G. In comparison to control groups, the major depression patient groups exhibited the highest percentage of 5-HT1A genotype CC, reaching 50%. These findings were supported by [23], which demonstrated a relationship between the CC genotype at this SNP and altered 5-HT1A receptor expression levels as well as decreased responsiveness to antidepressant treatment.

3. Association of serotonin receptor (5-HT1A) gene polymorphism with serotonin levels in psychological stress patients and control groups (Means ± SE).

In comparison to the genotype (GG) of the 5-HT1A receptor gene in the control group, the current study's findings revealed a substantial reduction ($p \leq 0.05$) in serotonin levels associated with the genotypes (GC, CC) of the 5-HT1A receptor gene. Nonetheless, No significant statistical difference was observed ($p \geq 0.05$) among the genotypes (GC, CC, and GG) of the 5-HT1A receptor gene and serotonin levels in the cohort of Alzheimer patients. Conversely, in the cohort of individuals with schizophrenia, there was a notable elevation ($p \leq 0.05$) in serotonin levels and the genotypes (GC, CC) of the 5-HT1A receptor gene relative to the genotype (GG) of the same gene. Furthermore, as seen in Table 7, there was no statistically significant difference ($p \geq 0.05$) among the genotypes (GC, CC, and GG) of the 5-HT1A receptor gene alleles and serotonin levels in the cohort of patients with severe depression.

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Table (7): Association of 5-HT1A receptor gene polymorphism with serotonin levels (means ± SE) in psychological stress patients and control groups

Groups	5-(HT1A) Gene	NO.	Serotonin level (pg/ml)
control group	GC	2	A38.99±14.25
	CC	5	A35.65±8.63
	GG	23	B50.51±3.72
Alzheimer Patients group	GC	10	A24.76±3.58
	CC	9	A26.39±4.96
	GG	1	A22.91±0.00
Schizophrenia Patients group	GC	10	A26.59±3.02
	CC	9	A21.23±4.76
	GG	1	B14.76±0.00
Major depression Patients group	GC	6	A22.28±2.36
	CC	10	A21.33±2.92
	GG	4	A26.92±2.39

Note: Distinct letters signify a statistically significant difference at (p≤0.05).

The findings of this study (Table 7) demonstrated a substantial elevation (p≤0.05) in serotonin levels, with the healthy group exhibiting the largest proportion (76.67%) of patients possessing the 5-HT1A genotype GG. Comparison of 5-HT1A receptor gene alleles (GC, CC) and serotonin levels with the 5-HT1A receptor gene allele (GG). In the comparison of serotonin levels between the Alzheimer patients group and the AHC group, there was no significant difference (p≥0.05) in the 5-HT1A receptor gene alleles (GC, CC, and GG). The findings demonstrated a substantial reduction (p≤0.05) in serotonin. Furthermore, as comparison to healthy groups, the cohort of Alzheimer patients had the largest proportion (50%) of the 5-HT1A genotype GC. These findings align with previous study [21], indicating that the (-1019) G allele and the 5-HT1A gene C (-1019) G polymorphism may serve as risk factors for AD. AD patients experienced a decrease in serotonin and 5-HIAA concentrations in the brain as well as the loss of postsynaptic 5-HT1A heteroreceptors and presynaptic somatodendritic 5-HT1A autoreceptors (24). When comparing the 5-HT1A receptor gene allele (GG) in the schizophrenia patient group to the healthy group, there was a significant increase (p≤0.05) in serotonin levels and serotonin receptor gene alleles (GC, CC). These results also revealed a significant decrease (p≤0.05) in serotonin levels. Additionally, compared to the AHC group, the schizophrenia patient group had the highest percentage of individuals with 5-HT1A genotype CC (65%). These results were consistent with the findings of [24], which demonstrated a correlation between the 5-HT1A gene and a decrease in serotonin levels based on the serotonin theory of schizophrenia, which states that cortical serotonin neurotransmission was decreased in patients with schizophrenia, while putamen,

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accumbens, and pallidus all showed enhanced serotonin neurotransmission. Additionally, individuals with schizophrenia demonstrated either reduced or stable 5-HT1A receptor density, maintained 5-HT6 receptor binding, and decreased 5-HT2 receptor density in the frontal cortex. Compared to the healthy group, the major depression patient group (table 7) showed a non-significant difference ($p \geq 0.05$) in serotonin levels and 5-HT1A receptor gene alleles (GC, CC, and GG). The results indicated a substantial reduction ($p \leq 0.05$) in serotonin levels. Furthermore, compared to healthy groups, major depression patient cohorts demonstrated the highest percentage of individuals with the 5-HT1A genotype CC (50%), a result that contradicts a study [25] This study reported altered expression levels of the 5-HT1A receptor and diminished response to antidepressant treatment linked to the CC genotype at this SNP. A polymorphism in the 5-HT1A regulating region (rs6295; G-1019C) has been linked to a heightened risk of depression and variations in brain receptor levels in genetic studies.

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Conflict of interests

There are non-conflicts of interest

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لخلاصة

المقدمة: يرتبط الاجهاد مع بعض الامراض النفسية مثل الزهايمر، الفصام والأكتئاب الشديد .ويعتقد ان هنالك ارتباط بين مستوى السيروتين المصلي والتغاير الجيني لمستقبل السيروتونين مع أعراض أمراض الاجهاد النفسية

طرق العمل: تهدف هذة الدراسة الى تحديد مستوى السيروتونين المصلي بواسطة المقايسة المناعية المرتبطة للانزيم المرتبط وعلاقة ذلك مع التغاير الجيني لمستقبل السيروتونين في القطعة الجينية rs6296G/C في 60 ذكرا" مريضا" بالأجهاد النفسي مقسمين الى 20 مريضا" لكل من الزهايمر ، الفصام والأكتئاب الشديد، بالأضافة الى 30 فردا" أصحاء ظاهريا" كمجموعة سيطرة.

الأستنتاجات: نستنتج من هذه الدراسة وجود علاقة بين التغاير الجيني لمستقبل السيروتونين ومستويات هرمون السيروتونين في مرضى الأجهاد النفسي (الزهايمر، الفصام والأكتئاب الشديد).

الكلمات المفتاحية: الأجهاد، الزهايمر، الفصام، الاكتئاب الشديد، مستوى السيروتونين، التغاير الجيني لمستقبل السيروتونين.

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