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# Association between serotonin receptor gene (HTR2A) polymorphisms (RS6313 and RS6311) with psychosis risk: A Case-Control study in Iraq

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**Abstract**

The serotoninergic system plays a crucial role in the pathogenesis of mental disorders. Accordingly, this study aimed to investigate the association between psychosis and the (rs6313, rs6311) polymorphisms of the 5HT2A gene. This study included 60 patients (35 males and 25 females) and 50 apparently healthy controls (22 males and 28 females). Blood samples were collected and then genomic DNA from White Blood Cells (WBCs) was extracted. The 5HT2A gene polymorphisms were characterized using PCR-RFLP technique. Statistical analysis showed a significant association between rs6313 polymorphism and patient with psychosis. In co-dominant odds ratio (OR) = 14.400, p=0.013 and dominant models (OR =0.082, p = 0.006), allele frequency analysis revealed the G allele was associated with increased risk of psychosis, whereas the A allele as a protective effect. Also, a significant association was observed (p = 0.05) aged 31–50 years among patients compared with controls. Regarding of rs6311 polymorphism , significant association were observed between patient and control groups under both recessive (p = 0.0001) and the co-dominant particularly for the T/T genotype (OR =6.399, p = 0.0001) and the C/T genotype (OR=10.750 p = 0.030).Regarding allele frequency analysis was showed a significate (p = 0.0001) between patients and controls that refers the C allele as a risk and the T allele as a protective effect .A significant difference association were observed)across sex (p = 0.036) and aged groups 10-30- and 31-50-year (p= 0.045 and p = 0.009, respectively)between patients and controls. The study indicates that the HTR2A rs6313 and rs6311 polymorphisms are significantly associated with risk of psychosis in Iraqi patients, particularly the C/T genotype and C allele of rs6311, as well as G allele frequency of rs6313, were found to be significantly associated with an increased susceptibility to psychosis. Moreover, the genetic variation (age and sex dependent) may contribute to the pathogenesis of psychosis.

**Keywords:** RS6311, RS6313, Psychosis, Serotonin, Tryptophan.

## Introduction

Psychosis is a constellation of symptoms resulting in a loss of touch with reality. Characterized by hallucinations, delusions, and disorganized behavior (Calabrese et al., 2023; Schrimpf et al., 2018). Psychosis is relatively common, with schizophrenia being the most prevalent form of psychotic disorder, affecting about seven in 1000 adults (Kuipers et al., 2014). Psychotic symptoms in childhood tend to be transient but they are linked with increased risk of psychotic disorders in adulthood (Fisher et al., 2013) (Broome et al., 2005; Kelleher, 2012).The typical onset of psychosis, with primary psychotic disorders most often emerging from the late teens to the early thirties (Gohar et al., 2023). Psychotic disorder more common in men than in women (Haverkampf, 2018).This difference seems to be attributable to a protective effect of estrogen (Häfner, 2003) (Calabrese & Al Khalili, 2023).

The risk of developing psychosis increases with the accumulation of many genetic risk variants and exposures to multiple adverse environmental factors. Additionally, the impact of environmental exposures likely depends on genetic factors, through gene–environment interactions(Zwicker, Denovan-Wright, & Uher, 2018) (Silverman et al., 2015; Zwicker, Fabbri, et al., 2018; Jam et al., 2025). Evidence suggests that amino acids, particularly the aromatic amino acids tyrosine and tryptophan, play a significant role in the etiology and pathophysiology of psychosis, due to their function as precursors of the key neurotransmitters(Li et al., 2022) (Panov & Panova, 2024). As tryptophan is essential amino acid precursor for serotonin obtained exclusively from the diet in the form of L-tryptophan (Li et al., 2024) (Yousef et al., 2024).Estimation of serum level may offer insight into the metabolism status of these neurotransmitter system. (Ghallab & Elassal, 2024; Naoi et al., 2025). That diet has been found to be a modifiable risk factor and an opportunity for intervention in many medical disorders and, more recently, in mental illnesses including unipolar

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depression (Aucoin et al., 2020).

Serotonin, a well-known neurotransmitter in the brain, also plays an important role in peripheral tissues, including the immune system. The neurotransmitter serotonin (5-HT) regulates many biological and behavior al processes in the body, including psychological processes in the Central Nervous System (CNS) and peripheral tissues including the gut and bones. (Liu et al., 2021; Sullivan, 2005; Wang et al., 2020).There is evidence that the neurotransmitter serotonin (5-Hydroxytryptamine; 5-HT) is implicated in psychosis pathophysiology. The serotonin hypothesis implicates excessive activation of *5-HT2A* receptors (Fišar, 2023), particularly those on glutamate neurons in the anterior cingulate cortex and dorsolateral frontal lobe in psychosis (Eggers, 2013). Gene of *5-HT2A* receptors was located on chromosome13(13q14-q21). It consists of 3 exons separated by 2 introns and it spans over 63 kb. It appears to have two alternative promoters, with a silencer element just downstream of the second promoter element .The *5-HT2A* receptor protein consists of 471 amino acids(Wu, 1999).

The 5-hydroxytrypamine (serotonin) 2A receptor *5-HTR2A* is the key receptor involved in the monoaminergic regulation of the body, which determines the biological functions and behavior of a person, and the target of the action of atypical antipsychotics. Polymorphic variants of the *HTR2A* gene rs6311 (-1438 A>G) and rs6313 (102 T>C), are the two most highly evaluated SNPs, which posit in the promoter region and exon 1 of *5-HTR2A*, respectively ,potentially associated with impairment of the effectiveness of posttranscriptional processes, are considered to be risk factors for neuropsychiatric and cognitive pathologies (Sujitha et al., 2014) (Lin et al., 2014), (Massoud et al., 2023) .The SNP at the promoter region (rs6311) has been shown to affect the promoter activity of the gene, leading to functional consequences. The inadequacy of the promoter activity (at rs6311)has been suggested to cause neuropsychiatric disorders including schizophrenia in several populations(Myers et al., 2007) (Abdolmaleky et al., 2011; Del Casale et al., 2025). Therefore, the replicative study aims to determine whether there is an association between psychosis among Iraqi patients and the (rs6313, rs6311) polymorphisms of *5HT2A*.

## Materials and Methods

### Clinical characteristics of the study group

The case-control study included a total 110 participants, comprising patients' diagnosis with psychosis were 60(35 males and 25 females) and 50 apparently healthy controls subjects was (22 males and 28 females). Patient samples were collected from individuals attending the Psychological Counseling Center at Al-Emam Al Sadeq hospital in Babylon Governorate and AL Alhassan Al Mujtaba hospital in Karbala Governorate as well as private clinics for psychiatric care between 15/9/2024 and 30/11/2024.

Diagnosis of patients were performed according to the "Diagnostic and Statistical Manual of Mental Disorder", fifth edition (DSM-5),published by the American Psychiatric Association (Association, 2013) .All diagnoses were made by a licensed psychiatric using standard clinical assessment procedures. The age of patients ranged from 15 to 65 years accordance to previously reported criteria (Gohar et al., 2023) .Exclusion criteria included Parkinson's disease, traumatic brain injury, cancer disease, autoimmune diseases, substance abuse and other major psychiatric or neurological disorders (EDITION, 1980) (Association, 2013) .The control groups consisted of healthy volunteers recruited from the hospital and university staff how were matched with the patient groups by age and sex. None of control subjects had a history of psychotic disorders or chronic medical condition. Psychiatric screening was performed through clinical interviews to confirm the absence of current or past psychiatric disorders. All participants shared similar ethnic and geographical backgrounds to minimize population stratification.

### Blood samples collection and Biochemical analysis

Venus blood samples were collected from all participants and divided into two parts: one part approximately 2 ml of blood was collected in to EDTA-containing tubes for genetic analysis. The second part included 3 ml of blood was storied in disposable gel tubes for serum separation. Serum tryptophan levels were measured according to the manufacturer's instructions using a Human

Tryptophan ELISA kit from (Bioassay Technology laboratory, CAT. No: E4244Hu).

## DNA extraction and amplification

Genomic DNA from (WBCs) was extracted by using DNA extraction kit (FAVORGEN- Korea) Lot, No:CD614123B16, (for frozen blood) according to the manufacturer's instructions. The purity and concentration of the extracted DNA were assessed obtained using a NanoDrop spectrophotometer device. DNA was evaluated by measuring Optical Density (OD) ratio at 260/280 nm DNA. The extracted gDNA was stored at -20C° for further molecular analyses.

The gene of *5HT2A* were characterized using PCR-RFLP technique. PCR amplification of *5HT2A* gene was performed by using thermal cycler (Cleaver Scientific, UK). Each PCR reaction was carried out in a total volume of 25µl, containing 1.25µl of each forward and reverse primers at 10 µM, 12.5µl of Green Master Mix (Promega, USA), 5µl nuclease-free water H2O and 5µl of DNA template. Primers used for the amplification reaction for rs6311and rs6313 were designed by Macrogen,lnc.(Korea), the primers sequence were as follows: For (rs6311) F: TCTGCTACAAGTTCTGGCTT, R: CTGCAGCTTTTTCTCTAGGG. For (rs6313) F: AAGCTGCAAGGTAGCAACAGC, R: CTGGGTGGCATATTTCTGCTG. PCR amplification protocols for both polymorphisms were as follow: Initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 30 secs, annealing at 58° C for 30 sec, extension at 72°C for 45sec, and final extension at 72° C for 7 min, hold 4°C for 10min.the PCR amplicons were visualized by electrophoresis on 1 % agarose gel stained with ethidium bromide and examined under ultraviolet illumination.

## Genotyping

Polymorphism of (rs6313 and rs6311) of 5-HT2A gene were genotyped using the Restrictions Fragment Length Polymorphism (PCR-RFLP) technique. The PCR products was digested with the restriction enzyme Mspl (Sib enzyme/Russia), according to the manufacturer's instructions to detect of single nucleotide polymorphism (SNPs) within the target sequence. The digestion reaction was performed in total volume 20µl, consisting of 0.25µl of digestive enzyme (Mspl), 4µl of appropriate reaction buffer,10.75µl of double-distilled water dH2O and 5µl of PCR product. The product were visualized via loading in 1.5%.agarose gel electrophoresis (Ajit et al., 2013). Electrophoresis was carried out at 85V,20 mA for 90 mins.

**Statistical analysis:** Distribution of genotypes and allele frequency for both patient and control groups were analyzed using Statistical Package for the Social Sciences (SPSS, 2019). To compare the differences in proportions, a chi-square ($\chi^2$) test was used, with p-values < 0.05 and < 0.01 set as significant. In addition, odds ratios (ORs) and their 95% Confidence Intervals (CIs) were computed to assess the strength and precision of association between the genetic polymorphism and the conditions investigated(George & Mallery, 2024) .

**Ethical approval:** The study protocol was reviewed and approved by the ethics Committee of the Department of Biology, College of Science, university of Babylon, Iraq. Project No: (B240901), Approval date (10/09/2024). All procedures involving humans participates were conducted in accordance with national and international ethical standards. Verbal informed consent was obtained from all participants or their legal guardians prior to inclusion in the study.

## Results

Demographic details collected from patients and controls included age, sex, family history, marital status, education levels and place of residence (Table 1). In this study, psychosis was more prevalent among individuals aged 31-50 years (47 %) followed by those aged 10-30 years (32 %) and aged 51-70 years (21%). The percentages of females were lower than that of males (42% and 58% respectively); however, this difference was not statistically significant. A statistically significate association was observed regarding the presence of a family history of psychosis (45%) compared with the control group (0.0%). Significant difference was also observed in education level findings (65% of psychosis with only primary education compared with controls 32%). In addition, higher proportions of single (41.7%) and separated (20%) individuals were observed among psychosis compared with controls.

**Table (1):** General characteristics of studied groups

| Variables | Control group | Psychosis group | p-value |
|---|---|---|---|
| | Mean±SD or No. (% ) | | |
| Total numbers | 50 | 60 | |
| Mean of age (year) | 35.9±2.7 | 38.8±4.2 | 0.712 (N.S) |
| Age (years) | | | |
| (10-30) years | 22(44%) | 19(32 %) | 0.412 (N.S) |
| (31-50) years | 19(38%) | 28(47 %) | |
| (51-70) years | 9(18%) | 13(21%) | |
| Total | 50 (100%) | 60 (100%) | |
| Sex | | | |
| Male | 22(44%) | 35(58%) | 0.134 (N.S) |
| Female | 28(56%) | 25(42%) | |
| Total | 50 (100%) | 60 (100%) | |
| Family history | | | |
| Present | 0(0%) | 27(45%) | 0.0001** |
| Absent | 50 (100%) | 33 (55%) | |
| Total | 50 (100%) | 60 (100%) | |
| Education level | | | |
| Primary | 16(32%) | 39(65%) | 0.003** |
| Secondary | 18(36%) | 11(18%) | |
| Bachelor's | 16(32%) | 10(17%) | |
| Total | 50 (100%) | 60 (100%) | |
| Place of residence | Urban Rural | | |
| Center | 30(60%) | 33(55%) | 0.598 (N.S) |
| Countryside | 20(40%) | 27(45%) | |
| Total | 50 (100%) | 60 (100%) | |
| Marital status | | | |
| Single | 13(26%) | 25(41.7%) | 0.001** |
| Married | 36(72%) | 23(38.3%) | |
| Separated | 1(2%) | 12(20%) | |
| Total | 50 (100%) | 60 (100%) | |

*Refer to significant association at (P≤0.05)

## Molecular analysis

PCR amplification the resulted in the appearance of distinct bands with amplicon sizes of 342bp and 427bp for rs6313 and rs6311, respectively (Figures 1and 2).


**Figure (1):** Agarose gel electrophoresis image of the 1% agarose gel for the PCR product of the target sequence of *5HT2A* (in exon 2 including rs6313) at 342bp.L represents the 100 bp marker, (1-9) Patient, (10-15) control group. Product run at 75V,20 mA for 60min

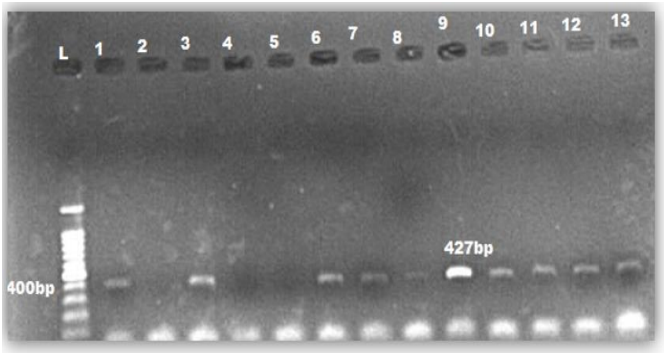


**Figure (2):** Agarose gel electrophoresis image of the 1% agarose gel for the PCR product of the target sequence of *5HT2A* (in promoter region including rs6311) at 427bp. L represents the 100 bp marker, (1-7) patient, (8-13) control. Product run at 75V, 20 mA for 60 min

RFLP and subsequent electrophoresis for the rs6313 (G > A polymorphism) at exon 2, the digested product of the wild type alleles (G/G) produced two fragments with sizes (126 and 216bp). However, one band with size 342 bp has been achieved after digestion the homo SNP alleles (A/A). For the heterozygous genotype (G/A) the electrophoresis photos showed three bands with sizes (342,126 and 216 bp) as seen in (Figure 3).

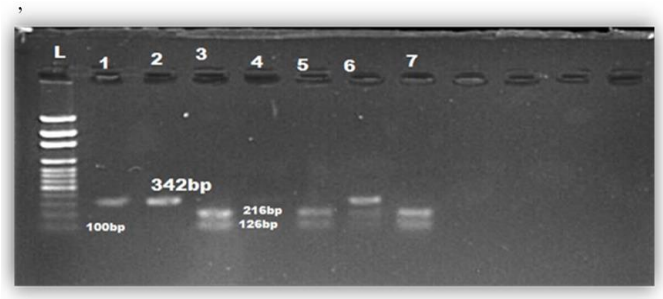


**Figure (3):** Agarose gel electrophoresis image of the PCR-RFLP products through rs6313 after digestion with *Msp*I enzyme. The photo shows different band sizes representing homo wild genotype (G/G) (126 and 216 bp) at samples (3,5and7). Homo SNP genotype (A/A) (342bp) at samples (1,2), heterozygous genotype (G/A) (342,126 and 216 bp) at sample (6). All samples run in 1.5 agarose at 85V,20mA for 90 mins. (L) represents the 100 bp marker

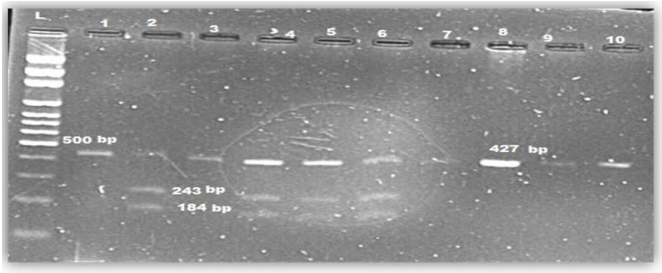


**Figure (4):** Agarose gel electrophoresis image of the PCR-RFLP products through rs6311 after digestion with *Msp*I enzyme. The photo shows different band sizes representing homo wild genotype (C/C) (243 and 184 bp) at samples (2). Homo SNP genotype (T/T) (427bp) at samples (1,7,8,9and 10), heterozygous genotype (C/T) (427,234 and 184bp) at sample (4,5and6). All samples run in 1.5 agarose at 85V,20mA for 90 mins. (L) represents the 100 bp

For the rs6311(C > T polymorphism) at promoter, the digested product of the wild type alleles (C/C) produced two fragments with sizes (184 and 243bp). However, one band with size 427bp has been achieved after digestion the homo SNP alleles (T/T). For the heterozygous genotype (C/T) the electrophoresis photos showed three bands with sizes (427,243 and 184 bp) as seen in (Figure 4)

The analysis of polymorphisms based on information from sequencing of rs6313 and rs6311 respectively (Figures 5and 6). First SNP rs6313 previously recorded in NCBI as Positionchr13:46895805 (GRCh38.p14) Alleles: G>A / G>C / G>T. While another SNP (rs6311) rpositionchr13:46897343 (GRCh38.p14) Alleles: C>A / C>T.

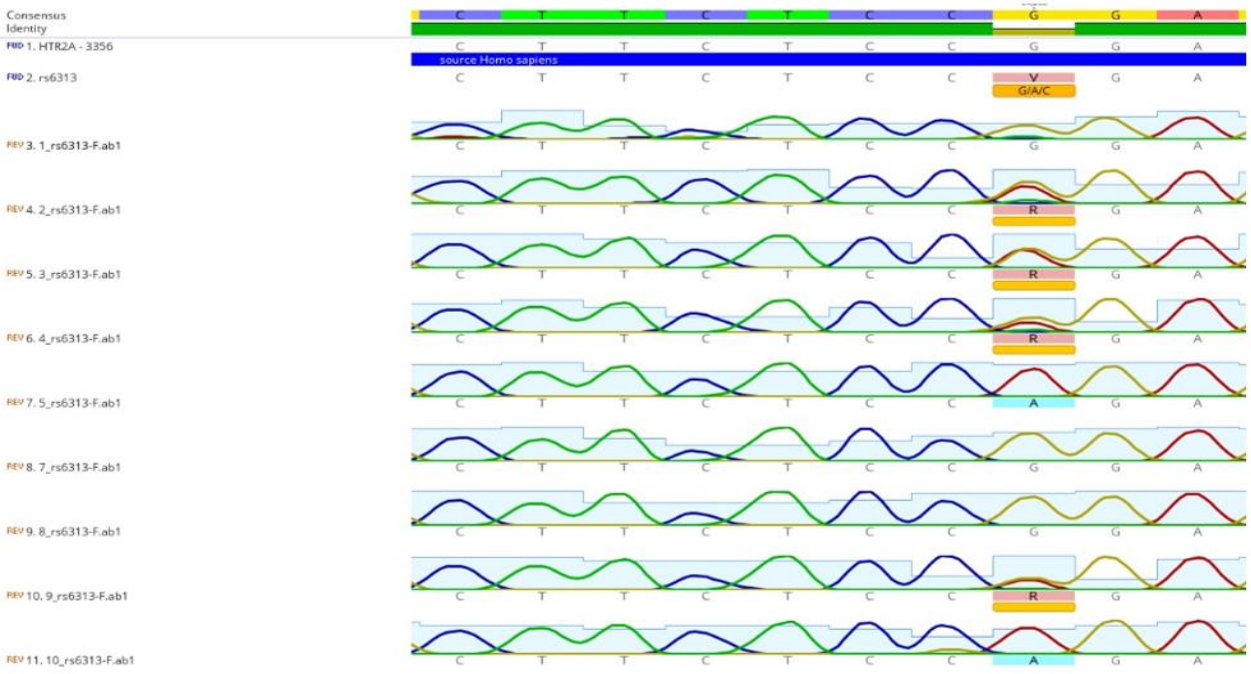


**Figure (5):** Analysis of *5HT2A* (rs6313) polymorphism based on information from sequencing

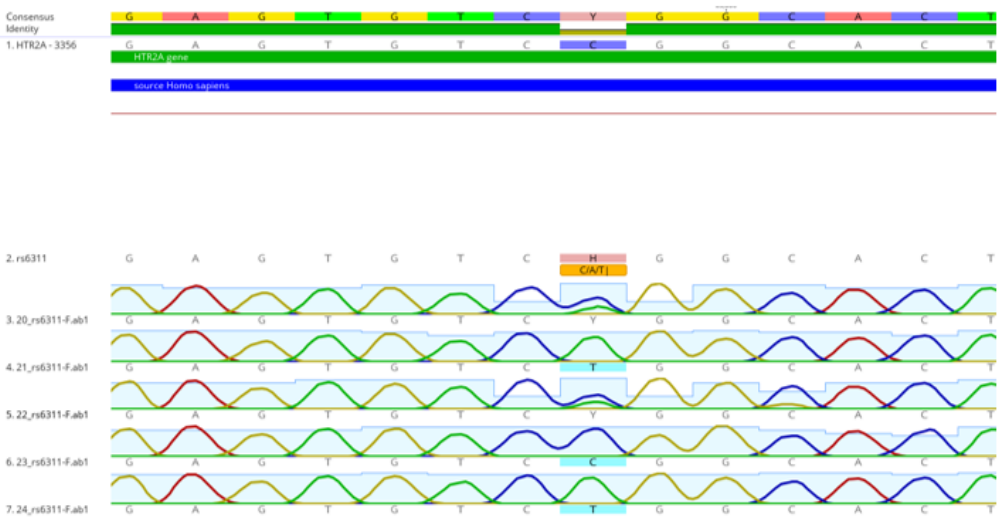


**Figure (6):** Analysis of *5HT2A* (rs6311) polymorphism based on information from sequencing

The result of rs6313 showed that, under the codominant model, the G/G genotype was more frequent among patients (20%) compared with controls (2%), with an odds ratio (OR) of (14.400), indicating a strong association between the G/G genotype and the risk of psychosis. The A/A genotype was more frequent in controls (60%) than in patients (41.6%), suggesting that A/A genotype may act as protective factors. The frequently of G/A genotype was not different between controls and patients.

Moreover, a statistically significant association (p = 0.006) was also detected under the dominant model. Furthermore, alleles frequency analysis revealed a significant difference (p = 0.004) was observed, a higher distribution of G allele among patients (0.39) compared with controls (0.21), whereas the A allele was more frequent among controls (0.79) compared with patients (0.61), these findings support the G allele as a risk factor, while A allele as a protective role against psychosis (Table 2).

**Table (2).** Genotyping and allele frequency of rs6313 polymorphisms between patients and control groups

| Rs6313g>A | Control | Patient | P-Value | Chi-Square | OR (CI 95%) |
|---|---|---|---|---|---|
| Codominant model | | | | | |
| GG | 1 (2%) | 12 (20%) | 1.00 | | |
| GA | 19 (38%) | 23 (38.4%) | 0.013* | 6.151 | 14.400(1.749-118.53) |
| AA | 30 (60%) | 25 (41.6%) | 0.364 | 0.823 | 1.453 (0.648-3.235) |
| Dominant model | | | | | |
| GG | 1(2%) | 12 (20%) | 0.006** | 8.479 | 0.082 (0.010-0.652) |
| GA+AA | 49 (98%) | 48 (80%) | | | |
| Recessive model | | | | | |
| GG+GA | 20 (40%) | 35 (58.4%) | 0.056 | 3.667 | 0.476(0.222-1.022) |
| AA | 30 (60%) | 25 (41.6%) | | | |
| Allele frequency | | | | | |
| G | 21 (0.21) | 47 (0.39) | 0.004** | 8.430 | 0.413 (0.225-0.0756) |
| A | 79 (0.79) | 73 (0.61) | | | |

*Refer to significant association at (P≤0.05)

The analysis of rs6311 showed that under the codominant model the C/C genotype was more frequent among patients (11.6%) than controls (2%). The C/T genotype was also more frequent in patients (41.6%), compared with control (12%) and a significant difference was observed (p = 0.030). Conversely, the T/T genotype was more frequent in controls (86%) than in patients (46.6%). In the recessive model (CC+CT vs T/T), the T/T genotype was more frequent in controls (86%) than in patients

(46.6%) and showed a significant difference (p = 0.0001). Regarding allele frequency, the C allele frequency was more frequent in patients (0.32) than in controls (0.08), whereas the T allele was substantially higher in controls (0.92) compared with patients (0.68). These findings indicate that, the C allele of rs6311 is strongly and significantly associated with psychosis in patients (Table 3).

**Table (3).** Genotyping and allele frequency rs6311 polymorphisms between patient and control groups

| Rs6311C>T | Controls | Patients | p-value | Chi-square | OR (CI 95%) |
|---|---|---|---|---|---|
| Codominant model | | | | | |
| C/C | 1(2%) | 7(11.6%) | 1.00 | | |
| C/T | 6(12%) | 25(41.6%) | 0.030* | 4.693 | 10.750 (1.254-92.164) |
| T/T | 43(86%) | 28(46.6%) | 0.0001** | 12.969 | 6.399 (2.330-17.571) |
| Dominant model | | | | | |
| C/C | 1(2%) | 7(11.6%) | 0.052 | 3.779 | 0.155 (0.018-1.302) |
| C/T+T/T | 49(98%) | 53(88.2%) | | | |
| Recessive model | | | | | |
| C/C+C/T | 7(14%) | 32(53.2%) | 0.0001** | 18.438 | 0.142 (0.055-0.367) |
| T/T | 43(86%) | 28(46.6%) | | | |
| Allele frequency | | | | | |
| C | 8 (0.08) | 39 (0.32) | 0.0001** | 19.489 | 0.181 (0.080-0.409) |
| T | 92 (0.92) | 81 (0.68) | | | |

* Refer to significant association at (P≤0.05)

The Case samples consisted of 35 males and 25 females, whereas control groups consisted of 22 males and 28 females. Although the G/G genotype was more frequent among male patients (25.7%) than in controls (4.5%). In contrast, the A/A genotype was more frequent among control groups for both sexes. The results showed that the frequency of rs6313 (G/G, G/A and A/A) genotypes in patients and controls revealed no statistically significant association across sexes (p > 0.05), (Table 4).

**Table (4)**. Distribution of (rs6313G>A) genotypes based on sex between patient and control groups

| (Rs6313 G>A) Sex | Groups | G/G | G/A | A/A | P-Value |
|---|---|---|---|---|---|
| | | No. (%) | | | |
| Male | Control | 1 (4.5) | 10 (45.5) | 11 (50) | 0.122 |
| | Patient | 9 (25.7) | 13 (37.1) | 13 (37.1) | |
| Female | Control | 0 | 9 (32.1) | 19 (67.9) | 0.107 |
| | Patient | 3 (12) | 10 (40) | 12 (48) | |

The distribution of rs6311 revealed that the (C/C and C/T) genotypes were more frequent in among patients compared with controls, whereas the T/T genotype was markedly higher in controls in both sexes. A significant was observed (p = 0.036 and p = 0.003) in male and females respectively among patients and controls, (Tables 5).

**Table (5).** Distribution of (rs6311C>T) genotypes based on sex between patient and control groups

| Sex | Groups | C/C | C/T | T/T | p-value |
|---|---|---|---|---|---|
| | | No. (%) | | | |
| Male | Control | 1 (4.5) | 4 (18.2) | 17 (77.3) | 0.036* |
| | Patient | 6 (17.1) | 14 (40) | 15 (42.9) | |
| Female | Control | 0 | 2 (7.1) | 26 (92.9) | 0.003** |
| | Patient | 1 (4) | 11 (44) | 13 (52) | |

*Refer to significant association at (P≤0.05)

In the present study, the ages of samples ranged from 15 to 65 years. The distribution of rs6313 genotypes

did not differ significantly between patients and controls in the 10-30 and 51-70-year age groups. However, a significant difference (p = 0.050) was observed in the 31–50-year age group among patients (Table 6).

**Table (6).** Distribution of rs6313 in (5-HT2A) genotypes based on age between patient and control groups

| (Rs6313g>A) Age Group | Group | G/G | G/A | A/A | p-value |
|---|---|---|---|---|---|
| | | No. (%) | | | |
| (10-30) year | Patient | 1 (5.3) | 9 (47.4) | 9 (47.4) | 0.530 |
| | Control | 0 | 10 (45.5) | 12 (54.5) | |
| (31-50) year | Patient | 10 (35.7) | 6 (21.4) | 12 (42.9) | 0.050* |
| | Control | 1 (5.3) | 7 (36.8) | 11 (57.9) | |
| (51-70) year | Patient | 1 (7.7) | 8 (61.5) | 4 (30.8) | 0.088 |
| | Control | 0 | 2 (22.2) | 7 (77.8) | |

*Refer to significant association at (P≤0.05)

The distribution of rs6311 genotypes (T/T, C/T, C/C) showed a significant difference between 10-30- and 31-50-year age groups (p = 0.045 and p = 0.009 respectively). The C/C and C/T genotypes were more frequent among patients across all age groups, while the T/T genotype was more frequent among controls (Table 7).

**Table (7).** Distribution of patients rs6311 in (5-HT2A) genotypes based on age between patient and control groups

| (rs6311C>T) Age groups | Group | C/C | C/T | T/T | p-value |
|---|---|---|---|---|---|
| | | No. (%) | | | |
| (10-30) year | Patient | 2 (10.5) | 7 (36.8) | 10 (52.6) | 0.045* |
| | Control | 0 | 3 (13.6) | 19 (86.4) | |
| (31-50) year | Patient | 4 (14.3) | 11 (39.3) | 13 (46.4) | 0.009** |
| | Control | 0 | 2 (10.5) | 17 (89.5) | |
| (51-70) year | Patient | 1 (7.7) | 7 (53.8) | 5 (38.5) | 0.120 |
| | Control | 1 (11.1) | 1 (11.1) | 7 (77.9) | |

*Refer to significant association at (P≤0.05)

## Biochemical study

The concentrations of Tryptophan were quantified in serum of both patients and controls.

**Table (8):** Variations in parameter between control and patient

| Parameters | Control | Patient | p-value |
|---|---|---|---|
| | Mean±S.D | | |
| Tryptophan | 25.5±6.7 | 33.3±4.6 | 0.021* |

*Refer to significant difference at (p≤0.05)

The results showed that tryptophan levels were significantly (p = 0.021) higher in patients than controls (33.3 and. 25.5 µM respectively), (Table 8).

**Table (9):** Variations in parameters between control and patient according to sex

| Parameters | Sex | Control | Patient | p-value |
|---|---|---|---|---|
| | | Mean±S.D | | |
| Tryptophan | Male | 20.21±4.4 | 37.94±2.9 | 0.0001** |
| | Female | 26.19±5.1 | 38.94±4.0 | 0.0001** |
| p-value | | 0.011* | 0.611 | |

*Refer to significant association at (P≤0.05)

The result of tryptophan levels according to sex are displayed in (Table 9). Both male and female patients (37.94 and 38.94 respectively) exhibited significantly (p=0.0001) higher tryptophan levels compared with controls (20.21for male and 26.19 in female group), however, the sex effect differed with the difference being more pronounced in males.

According to the age groups, the results revealed that, the aromatic amino acid tryptophan significantly elevated in patient compared with controls across different age groups of, particularly in the 31-50- and 51-70-year age groups (p= 0.002 and p= 0.005 respectively), the highest increase was in the older group of patients (Table 10).

**Table (10):** Variations in parameters between control and patient according to age groups

| Parameters | Age groups (year) | Control | Patient | p-value |
|---|---|---|---|---|
| | | Mean±S.D | | |
| Tryptophan | 10-30 | 25.72±4.5 | 26.38±9.2 | 0.612 |
| | 31-50 | 24.58±8.8 | 35.56±4.4 | 0.002** |
| | 51-70 | 26.95±5.6 | 40.00±3.9 | 0.005** |

*Refer to significant difference at (p≤0.05)

## Discussion

The etiology of psychosis is complex and multifactorial, involving a combination of biological, psychological, and environmental factors (Khanna, 2025).Accumulated exposure to stress can trigger a cascade of neural, developmental, and hormonal sequelae that ultimately contribute to the onset of psychotic disorder (Daskalakis et al., 2012; Pruessner et al., 2017; Vargas et al., 2019; Walker et al., 2008). Environmental insults during early life may lead to aberrant brain development, thereby increasing predisposes to the later onset of psychosis (Broome et al., 2005). The present results showed non-significant differences were observed between patients and controls among age, sex consists of with a previous Iraqi study also, did not showed significant among age, sex between schizophrenia subjects and controls (Khudhiar & Saud, 2019).

In the current study, psychosis was most prevalent among individuals aged 31-50 years (47 %) , followed by those aged10-30 years (32 %),findings consistent with previous reports (AFONSO et al., 2021; Charlson et al., 2018).Furthermore, a higher age as well as a more advance in loss of socio-

economic connection status is highly associated with schizophrenia (Häfner, 2018). In the present sample, the proportion of females was lower than that of males, however this difference was not statistically significant. Due biologic, hormonal and psychological factors have been processed to account for the higher prevalence of psychosis observed in men compared with women (Riecher-Rössler et al., 2018).

In regarding to family history of psychosis, 27 patients (45%) reported a positive family history ,whereas no case recorded in the control group(0.0%).Social determinants may have an individual impact on psychosis, as well as through exacerbating individual vulnerabilities such as neurobiological factors and genetic predispositions (Selloni, 2024). This findings agreement with previous studies (Haverkampf, 2018; Legge et al., 2025).

In psychosis lower educational attainment is consistently reported. Early onset of symptoms during adolescence or early adulthood often disrupts academic achievement (Morgan et al., 2014). High percentage (65%) of psychosis people with only primary education. Also, current results displayed higher proportions of single (41.7%) and separated (20%) percentages in psychosis group compared with controls (26%) and 1(2%) respectively. Psychotic disorders are more likely in People to be single, separated, or divorced, reflecting difficulties in maintaining stable social and marital relationships (Marwaha et al., 2014) (Marwaha et al., 2007) (Ohlhoff et al., 2025).

The 5-hydroxytryptamine 2A receptors gene (*HTR2A*) encodes the *5-HT2A* receptor ,Which is activated by serotonin (Hoyer et al., 1994). They are expressed at high levels on pyramidal cells of the prefrontal cortex, where they are ideally positioned to modulate both cognitive functions, such as working memory or executive control, and also emotions (Weber & Andrade, 2010).In this context, the genes coding serotoninergic receptors have been associated with various psychopathologies (Sinopoli et al., 2017) (Soga et al., 2021).

The present study demonstrated an association between rs6313 and rs6311 polymorphisms and the risk of psychosis. These findings are consistent with a previous study which showed associations of rs6311/rs6313 with schizophrenia (Del Casale et al., 2025; Morozova et al., 2024). Also, Qadeer and et al demonstrated an association between serotonin system-related genes and homicidal behavior and criminal aggression in a prison population of Pakistani origin (Qadeer et al., 2021). The analysis of rs6313 indicating that the A allele may be as protective, whereas the G allele is associated with an increase of psychosis incident among the studied Iraqi samples, whereas findings of rs6311 indicates that, the C allele is strongly and significantly associated with psychosis in Iraqi patients. While the TT genotype may act as protective factor against the psychosis. However, these findings contrast with several previous studies. For examples the studies by (Tan et al., 2014) (Yildiz et al., 2013) did not support the hypothesis that the T102C and 1438 A/G polymorphisms of the *5-HT2A* receptor gene are associated with schizophrenia.

Functionally the rs6311polymorphism has been linked to altered promoter activity, potentially modifying *HTR2A* expression levels (Polesskaya & Sokolov, 2002) . The rs6313 responsible for serotonin reuptake, among other functions, In the Russian population associations of HTR2A rs6313(G>A) with schizophrenia in patients from the schizophrenia group separately compared to the control group were also found (Morozova et al., 2024).The evidence showing that the production of the C-allele form of *HTR2A* is significantly less than that of the T-allele form in normal controls and schizophrenic patients. Although the association of schizophrenia with the C allele of *HTR2A* (Abdolmaleky et al., 2004).Moreover a previous study reported that (rs6311:T) marker was protective against suicidal behavior.CC-homozygotes for the functional SNP rs6311 reported more anger- and aggression related behavior (Giegling et al., 2006; Waltes et al., 2016). The rs6313 polymorphism is associated with schizophrenia in studies in which the minor allele is C (Sun et al., 2017).Additionally ,rs6311 has been associated with psychosis risk and antipsychotic response (Serretti et al., 2007).

The present results indicate that the rs6313 polymorphism does not differ significantly by sex ,whereas the rs6311 polymorphism showed a significate differences, among Iraqi psychosis patients and controls according to sex .Some earlier reports have suggested potential sex-specific associations ;however, these results have not been consistently reproduced (Abdolmaleky et al., 2004; Massoud et al., 2023; Yang et al., 2014). Moreover, (Liu *et* al., 2022) reported a significant differences in sex in psychiatric symptoms and cognitive function between schizophrenia patients with and without depressive symptoms. In contrast the studies have reported no sex differences in psychotic symptoms (Addington et al., 1996; Huber et al., 1980).

These findings suggest that rs6313 is associated with psychosis through the G/G genotype in the 31–50-year age group, whereas rs6311 is associated with psychosis through the (C/C and C/T) genotypes in the 10-30- and 31-50-year age groups of the *5-HT2A* gene polymorphism. These results are consistent with studies suggesting a possible link between *5-HT2A* polymorphisms and age at onset in specific populations (Tsuang *et* al., 2013). Study performed in Iraq by Noor and Asmaa found an association between rs643627 polymorphism of *5-HT2A* gene and age and gender in schizophrenia patients' group(Khudhiar & Saud, 2019).In contrast that in Iranian study no significant difference in age average between schizophrenic patients and healthy controls (Massoud *et* al., 2022)

Present findings indicate that tryptophan levels were significantly ($p = 0.021$) higher in patients than controls (33.3 vs. 25.5 μM respectively). Previous studies have reported elevated plasma tryptophan levels in patients with schizophrenia accompanied by abnormalities in tryptophan metabolism and serotonin synthesis (Almulla et al., 2022; Chiappelli et al., 2014; Möller et al., 2012). However, these results are inconsistent with finding reporting a reduced tryptophan to large-neutral amino acid ratio in the serum of schizophrenia(Garip et al., 2024) .Such discrepancies likely reflects the heterogeneity of psychosis, as well as the influence of antipsychotic medication, nutritional status and methodological differences including sample type (plasma vs. serum) and fasting conditions(fasting vs. non-fasting sample) (Garip et al., 2024).

With respect to sex-related difference in serum tryptophan levels, a more pronounced effect was

observed in males. Differences in amino acid metabolism are well documented and are influenced by sex hormones and differential enzyme activity (Lin et al., 1959).Estrogen, for instance, modulates tryptophan hydroxylase (TPH) (Yang et al., 2019).Consistent evidence suggests that women may be more susceptibility than men to fluctuations in the availability of its precursor Tryptophan )Pais et al., 2023.( Accordingly, postmenopausal women with reduced levels of estrogen may exhibit decreased TPH gene expression or diminished enzymatic activity, leading to reduced central serotonin(5-HT) synthesis and availability. This reduction may contribute to an increased vulnerability to mood and eating disorders in postmenopausal women (Xu et al., 2025).According to the age-groups stratification, serum tryptophan levels showed the highest increase was in the older group of patients , these findings are in line with previous studies displayed that chronic schizophrenia and aging are associated with alternations in kynurenine pathway activity ,as well as cumulative effects of long-term antipsychotic exposure (Kuuskmäe et al., 2023).Moreover, dietary factors, influence age-related neurodegeneration and cognitive decline, and bioactive compound derived from plant-based food have been proposed as potential neuroprotective agents (Ki et al., 2024).

## Conclusions

Genotyping analysis of *5HT2A* gene revealed that the rs6311 polymorphism particularly the C/T genotype and the C allele, as well as the rs6313 polymorphism, especially G allele frequency, are associated with psychosis in Iraqi patients. However, the tryptophan biomarker results remained inconsistent.

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