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# Cannabinoid Receptor 1 (CNR1) Gene Polymorphisms in Schizophrenia Patients: Rs6454674 Polymorphism is Associated with Disease Severity

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**ABSTRACT:**

Cannabinoid receptor 1 (CNR1) gene polymorphisms in schizophrenia patients: Rs6454674 polymorphism is associated with disease severity

**Objective:** The endocannabinoid system contributes to the regulation of emotions, stress, memory, and cognition. It has been reported that endocannabinoids cause GABAergic inhibition and dopaminergic increase in the mesolimbic and nigrostriatal systems, thus playing a part in the neurobiology of schizophrenia. In this study, we investigate cannabinoid receptor 1 (CNR1) gene polymorphisms in schizophrenia patients.

**Methods:** CNR1 gene polymorphisms were studied in 66 schizophrenia patients and 65 healthy controls. To obtain genomic DNA, proteinase K digestion and the salt-chloroform method were used. Clinical Global Impression severity scale (CGI-S) and Positive and Negative Syndrome Scale (PANSS) were administered to evaluate the severity of schizophrenia symptoms. CNR1 gene polymorphism was determined by using polymerase chain reaction (PCR), Restriction Fragment Length Polymorphism (RFLP), and Single Strand Conformation Polymorphism (SSCP) methods for the Rs6454674, Rs806368, and Rs1049353 sites.

**Results:** There was no difference in CNR1 gene polymorphisms between schizophrenia patients and control groups (Rs6454674 T/G; p=0.973, Rs806368 T/C; p=0.349, Rs1049353 A/G; p=1.00). However, CGI-S, PANSS total, PANSS positive, PANSS negative and PANSS general psychopathology scores were significantly lower in schizophrenia patients with RS6454674 polymorphism than in those not showing polymorphism.

**Conclusion:** Our results suggest that CNR1 gene polymorphisms may be associated with clinical symptoms and disease severity in schizophrenia patients.

**Keywords:** schizophrenia, cannabinoid, receptor, polymorphism

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## INTRODUCTION

It is thought that schizophrenia is caused by a combination of multiple factors such as genetic, biological, environmental, and psychological. According to this view, people might have a genetic predisposition for schizophrenia, but the disease may not emerge if some other factors are not added. These factors are birth complications that can cause mutagenesis or a change in gene expression, biological factors such as nutrition, and to a lesser extent, certain environmental factors including psychological ones[1].

The endocannabinoid system contributes to the regulation of memory, cognition, emotions, and stress[2]. In addition, it contributes to a spectrum of personality traits in normal individuals and a susceptibility to mood disorders[3]. CNR1 receptors are highly expressed in the hippocampus, cerebellum, basal ganglia, and neocortex of the brain[4]. CNR1 receptors are the primary cannabinoid receptors in the brain. The CNR1 receptor is a

presynaptic metabotropic receptor that bounds to G proteins. As a result of activation of these receptors, inhibition of neuronal depolarization, diminished action potential production, and reduced excitatory or inhibitory neurotransmitter release occur, which cause a decrease in impulse transmission[3-5]. Endogenous cannabinoids have been found to be higher in the cerebrospinal fluid of schizophrenic patients[6]. It has been reported that endocannabinoids cause GABAergic inhibition and dopaminergic increase in the mesolimbic and nigrostriatal systems, thus playing a role in the neurobiology of schizophrenia[7].

CNR1 receptors are encoded by the CNR gene located on chromosome 6q14–q15[8]. The CNR1 locus has several single nucleotide polymorphisms and an (AAT)n microsatellite[9]. The CNR1 gene is associated with the modulation of the release of several monoamine neurotransmitters that regulate the excitatory and inhibitory synaptic transmission cycles. It is proposed that CNR1 receptors contribute to the regulation of mood and cognition, and the brain endocannabinoid system takes part in the etiopathogenesis of many psychiatric disorders[10].

There is limited research regarding CNR1 gene polymorphism in schizophrenia. In our study, we investigated CNR1 gene polymorphisms in patients with schizophrenia.

## METHODS

### Study Population

CNR1 gene polymorphisms were studied in 66 schizophrenia patients who presented to the Psychotic Disorders Unit of the Department of Psychiatry, School of Medicine, Gaziantep University, and were diagnosed with schizophrenia according to the 4th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV). Patients with any other kind of axis I psychiatric disorders and with known major health problems, diabetes, and malignancies were excluded from the study. The control group consisted of 65 healthy subjects matched with the patients in terms of age and gender who had no history of any psychiatric disorder or major health problems.

The study was approved by the local ethics committee in accordance with the Declaration of Helsinki. Informed consents were obtained from all the study participants before enrollment.

### Data Collection

A sociodemographic data form was completed, including the patient's age, gender, educational level, marital status, job, smoking, history of ECT, illness and hospitalization, disease duration, received treatments, height and weight, and body mass index. Clinical Global Impression severity scale (CGI-S)[11] and Positive and Negative Syndrome Scale (PANSS)[12] were administered to evaluate the severity of schizophrenia symptoms. Physical and neurological examinations were performed for each of the patients and controls.

### DNA Isolation and Polymorphism Analysis

Two mL venous blood samples of patients and controls were collected into sterile Vacutainer tubes containing EDTA in order to purify genomic DNA, using proteinase K digestion and the salt-chloroform method[13]. Genomic DNA samples were stored at -20°C until being processed with these applications. Amplification of DNA samples was achieved by using AB Thermal Cycler (ABI Inc. CA, USA). Amplified PCR products were visualized by using ethidium bromide stain in 2% agarose. Restriction Fragment Length Polymorphism analysis was conducted by digesting the PCR products with HpyCH4III and BseGI enzymes for the rs6454674and rs806368 restriction sites, respectively. Restriction fragments were analyzed after resolving the bands in 3% agarose. Studied CNR1 gene polymorphisms, primer sequences, sizes of the amplicons, and annealing temperatures are presented in Table 1. For rs1049353, Single-Strand Conformation Polymorphism analyses were performed on 7% acrylamide/bisacrylamide gel with a ratio of 49:1 as previously described[14]. All SSCP gels were neutralized with low-concentrated acetic acid and

visualized by silver staining. Sanger (dideoxy) sequencing analysis was performed for some of the samples in order to verify the variations within them.

All statistical analyses were carried out by using GraphPad Prism (v6.02, GraphPad Software Inc., San Diego, CA, USA) and SPSS (v16.0) packages. Student-Newman-Keuls test for more than two groups was used and for the significance in the genotype and allele frequency differences the $\chi^2$ test or Fisher's exact tests were applied. Haplotypes under 3% population frequency were excluded. Chi-square or Fisher's exact test were used to compare the categorical variables. The Kolmogorov-Smirnov test was used to test normal distribution. To compare the continuous variables, the non-parametric Mann-Whitney U-test was used for not normally distributed variables, and Student T test was used for normally distributed variables. Overall, applied tests were two-tailed and $p<0.05$ was considered as significant.

**Table 1: Studied CNR1 gene polymorphisms, primer sequences, sizes of the amplicons, and annealing temperatures**

| Reference SNP no | Primer Sequences (5'→3') | Expected size of PCR product (bp) | Annealing temperature (°C) |
|---|---|---|---|
| rs6454674F: | F: ATGCAACTGAGCTAACATGGAAT<br>R: ACGGGGAAATTTAGACAGGCTT | 510 | 58 |
| Rs806368 | F: GTTTCCCGCTTGAAACATTGGA<br>R: GAAATAGGCCCAACCACCAGA | 510 | 59 |
| Rs1049353 | F: GATCATGGTGACAATCACCTTTTCA<br>R: TGCGCAGCCTCTGGATAAC | 300 | 57 |

F: Forward, R: Reverse

**Table 2: Some socio-demographic and clinical characteristics of the study population**

| | Schizophrenia patients (n=66) | Healthy Controls (n=65) | p |
|---|---|---|---|
| **Age** | 36.21±10.0 | 35.3±10.3 | p=0.647 |
| **Gender** | | | p=0.491 |
| Male | 43 (65.2%) | 46 (70.8%) | |
| Female | 23 (34.8%) | 19 (29.2%) | |
| **Working status** | | | p<0.001 |
| Working | 7 (10.8%) | 49 (74.2%) | |
| Not working | 58 (89.2%) | 31 (25.8%) | |
| **Smoking** | | | p<0.001 |
| Yes | 40 (60.6%) | 12 (18.5%) | |
| No | 26 (39.4%) | 53 (81.5%) | |
| **Body Mass Index** | | | p=0.491 |
| Obese | 43 (65.2%) | 46 (70.8%) | |
| Non-Obese | 23 (34.8%) | 19 (29.2%) | |
| Disease duration (mean±sd) | 11.8±8.8 | | |
| **Type of illness** | | | |
| Paranoid | 48 (36.6%) | | |
| Disorganized | 14 (10.7%) | | |
| Catatonic | 2 (1.5%) | | |
| Residual | 2 (1.5%) | | |
| **Hospitalization** | | | |
| Yes | 52 (78.8%) | | |
| No | 14 (21.2%) | | |
| **Comorbidity** | | | |
| No | 51 (77.3%) | | |
| Major depression | 8 (12.1%) | | |
| Anxiety disorder | 3 (4.6%) | | |
| Epilepsy | 1 (1.5%) | | |
| Mild mental retardation | 2 (3.0%) | | |
| Tourette syndrome | 1 (1.5%) | | |

## RESULTS

Age and gender distributions of the groups were similar (p=0.647; p=0.491, respectively). Sociodemographic and some clinical characteristics of the study population are shown in Table 2.

The distribution of the CNR1 Rs6454674 (T/G), and Rs806368 (T/C) genotypes did not deviate from the Hardy-Weinberg equilibrium in either healthy controls or schizophrenia patients, but the Rs1049353 (G/A) genotype deviated in both study groups. There was no difference in CNR1 gene polymorphisms between schizophrenia patients and control groups (Rs6454674 T/G; p=0.973, Rs806368 T/C; p=0.349, Rs1049353 A/G; p=1.00). The polymorphism and allele comparisons for the groups are presented in Table 3 and Table 4.

CGI-S, PANSS total, PANSS positive, PANSS negative and PANSS general psychopathology scores were significantly lower in schizophrenia patients with RS6454674 polymorphism than those without a polymorphism (Table 4). There were no differences between non-obese and obese patients in the study group with respect to polymorphisms (Rs6454674 p=0.933, Rs806368 p=0.597).

**Table 3: Comparison of polymorphisms and alleles according to the study groups**

| Rs6454674 | Genotype/Allele | | Control n=65 (%) | Patient n=62 (%) | p | OR (95% CI) |
|---|---|---|---|---|---|---|
| | Genotype | TT | 47 (72.4) | 45 (72.6) | | |
| | | TG | 9 (13.8) | 13 (20.9) | 0.479 | 1.51 (0.65-3.51) |
| | | GG | 9 (13.8) | 4 (6,5) | 0.021 | 0.46 (0.14-1.5) |
| | Allele | T | 103 (79.2) | 103 (83.1) | | |
| | | G | 27 (20.8) | 21 (16.9) | 0.528 | 0.78 (0.40-1.53) |
| | $\chi^2$ | | 21.81 | 4,02 | | |
| | HWE | No | No | | | |
| **Rs806368** | **Genotype/Allele** | | **Control n=61 (%)** | **Patient n=59 (%)** | **p** | **OR (95% CI)** |
| | Genotype | TT | 29 (47.5) | 23 (39.0) | | |
| | | TC | 31 (50.8) | 34 (57.6) | 0.457 | 1.38 (0.71-2.68) |
| | | CC | 1 (1.7) | 2 (3.4) | 0.585 | 2.52 (0.30-21.1) |
| | Allele | T | 89 (72.9) | 80 (67.8) | | |
| | | C | 33 (27.1) | 38 (32.2) | 0.399 | 1.28 (0.71-2.30) |
| | $\chi^2$ | | 5,05 | 6,03 | | |
| | HWE | | No | No | | |
| **Rs1049353** | **Genotype/Allele** | | **Control n=61 (%)** | **Patient n=57 (%)** | **P** | **OR (95% CI)** |
| | Genotype | AA | 0 | 0 | | |
| | | AG | 61 (100.0) | 57 (100.0) | 1.00 | |
| | | GG | 0 | 0 | | |
| | Allele | A | 61 (50.0) | 57 (50.0) | | |
| | | G | 61 (50.0) | 57 (50.0) | 1.00 | 1.00 (0.58-1.71) |
| | $\chi^2$ | | 61 | 57 | | |
| | HWE | | No | No | | |

HWE: Hardy-Weinberg equilibrium, $\chi^2$: chi square value

**Table 4: Polymorphism (homozygous or heterozygous) status of the study population**

| | Schizophrenia patients | Healthy controls | p |
|---|---|---|---|
| **Rs6454674 polymorphism** | | | 0.973 |
| Yes (n, %) | 17 (27.4%) | 18 (27.7%) | |
| No (n, %) | 45 (72.6%) | 47 (72.3%) | |
| **Rs806368 polymorphism** | | | 0.349 |
| Yes (n, %) | 36 (60.1%) | 32 (52.5%) | |
| No (n, %) | 23 (38.9%) | 29 (47.5%) | |

**Table 5: Comparison of PANSS and CGI-S scores, some socio-demographic and clinical characteristics of patients according to polymorphism status**

| | rs6454674 | | p | rs806368 | | p |
|---|---|---|---|---|---|---|
| | Polymorphic (n=17) | Non-Polymorphic (n=45) | | Polymorphic (n=36) | Non-Polymorphic (n=23) | |
| Age (mean±SD) | 33.3±9.8 | 36.6±9.6 | 0.508 | 35±5 9.7 | 37.3±11.1 | 0.484 |
| Gender | | | 0.455 | | | 0.250 |
| Male | 10 (58.8%) | 31 (68.9%) | | 27 (75.0%) | 14 (60.9%) | |
| Female | 7 (41.2%) | 14 (31.1%) | | 9 (25.0%) | 9 (39.1%) | |
| BMI | | | 0.933 | | | 0.597 |
| Obese | 10 (58.8%) | 27 (60.0%) | | 21 (58.3%) | 15 (65.2%) | |
| Non-Obese | 7 (41.2%) | 18 (40.0%) | | 15 (41.7%) | 8 (34.8%) | |
| Duration of illness (median, min-max) | 8 (1-36) | 10 (1-299 | 0.627 | 10 (1-36) | 10 (1-29) | 0.907 |
| CGI-S (median, min-max) | 2 (1-6) | 5 (1-7) | 0.001 | 3 (1-7) | 5 (1-7) | 0.277 |
| PANSS positive (median, min-max) | 11 (7-25) | 20 (7-42) | 0.004 | 13 (7-39) | 21 (7-42) | 0.145 |
| PANSS negative (median, min-max) | 12 (7-27) | 17 (7-42) | 0.003 | 14 (7-41) | 16 (7-42) | 0.157 |
| PANSS general (mean±SD) or (median, min-max) | 25.4±9.9 | 38.1±16.4 | 0.003 | 31 (16-73) | 33 (16-75) | 0.413 |
| PANSS total (mean±SD) or (median, min-max) | 49±0 18.5 | 78.1±33.4 | 0.001 | 62 (30-129) | 71 (30-154) | 0.309 |

There were no significant differences between each polymorphism and the characteristics of age, gender, body mass index, and duration of illness (Table 5).

## DISCUSSION

The major finding of our study is the relationship between disease severity and rs6454674 polymorphism in patients with schizophrenia. Clinical parameters such as CGI-S, PANSS total, PANSS positive, PANSS negative and PANSS general psychopathology scores were significantly lower in schizophrenia patients with RS6454674 polymorphism than in those with no polymorphism. To our knowledge, there is no other research evaluating the relationship between clinical parameters of schizophrenia and rs6454674 polymorphism.

Various theories have been proposed to explain the relationship between cannabis use and schizophrenia. It has been suggested that patients with schizophrenia use cannabis for self-medication, or that psychosis arises as a result of the use of cannabis, or that there are genetic and biological similarities between schizophrenia and cannabis use disorder[15,16]. But as a result it has been clarified that use of cannabis is a risk factor for the onset of schizophrenia especially in vulnerably people[17].

On the basis of these present data, it is hypothesized that the endocannabinoid system (ECS) plays a role in schizophrenia. In accordance with this hypothesis, endocannabinoid levels were studied in cerebrospinal fluid (CSF) and blood of schizophrenia patients. These studies show increased cannabinoid levels in CSF and blood of schizophrenics, and it is suggested that ECS alterations play a part in the pathophysiology of schizophrenia[6,18,19]. However, genetic studies have not shown this relationship definitively. CNR genes in schizophrenia have been studied with various methods. But results are conflicting and do not support the relationship between ECS and schizophrenia obtained from CSF and blood studies[20].

In one study, it has been shown that the frequency of rs1049353 polymorphism of the CNR1 gene is higher in non-responding schizophrenia patients; yet in the same study, there were no differences in the frequency of rs1049353 polymorphism between patients and controls[21].

We also found that there were no differences in CNR1 gene polymorphisms between schizophrenia patients and healthy controls. Our finding is consistent with previous studies that did not find any relationship between CNR1 gene polymorphisms and schizophrenia[21-26].

In a study that examined the distribution of

allelic AAT repeats and genotypic 1359G/A polymorphisms in the CNR1 gene in schizophrenia patients, it has been shown that there is no difference in terms of genotypic polymorphisms between patients and controls, supporting our study results. But in the cited study, a significant association was found between allelic AAT repeat polymorphism of the CNR1 gene and schizophrenia, and this association was in the hebephrenic type, whereas it was not found in the paranoid type[27]. There are some studies that show a difference between AAT repeat polymorphism in the CNR1 gene and schizophrenia patients[7,28]. But in contrast to these, some other studies show no difference in allelic AAT repeat polymorphism of the CNR1 gen between schizophrenic patients and controls[22,23].

Small sample size is a major limitation of our study. In conclusion, our results suggest that there may be an association between CNR1 gene polymorphisms and clinical symptoms and disease severity in schizophrenia patients.

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