

Role of miRNA Gene Variants (miR-22 and miR-155) as the Factors Affecting Susceptibility to Panic Disorder

Zeynep Yegin¹, Gokhan Sarisoy², Ahmet Uzun², Haydar Koc³

¹Medical Laboratory Techniques Program, Vocational School of Health Services, Sinop University, Sinop, Turkey

²Department of Psychiatry, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

³Department of Statistics, Faculty of Science, Cankiri Karatekin University, Cankiri, Turkey

Objective: Variants within genes encoding microRNAs (miRNAs) may alter the expression of both miRNAs and their target genes, thus contributing to the etiology of psychiatric disorders. The involvement of miRNAs in neuronal differentiation and synaptic plasticity supported this hypothesis. We aimed to investigate the links between miR-155 rs767649/miR-22 rs8076112 and the risk of panic disorder (PD) in a sample of Turkish population.

Methods: In this experimental study, 134 PD patients and 140 healthy controls were recruited. Genotyping was carried out using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method. To evaluate PD phenotypes, Panic Disorder Severity Scale (PDSS) was also administered to patients to clarify possible associations between the scale and risk variants analyzed.

Results: The genotype analysis of miR-155 rs767649 did not show an association with PD risk and it was not related to the disease severity. For miR-22 rs8076112 variant, a statistically significant association was determined; CC genotypes were lower in patients compared to controls. Logistic regression analysis proved the highly protective effect (80.4%) of CC genotype against PD ($p = 0.041$; OR = 0.196, 95% CI = 0.041–0.934). Though its significance in disease liability, miR-22 rs8076112 was not associated with the disease severity.

Conclusion: Our findings firstly report the combined analysis of miR-155 rs767649 and miR-22 rs8076112 in PD in terms of both disease susceptibility and severity. These findings await replication in independent cohorts with enrichment of other miRNA gene variants. Thus, certain miRNAs and their target genes involved in the etiology and phenotypes of PD could be enlightened.

KEY WORDS: Panic disorder; MicroRNA; Genetic association; miR-22; miR-155; Panic Disorder Severity Scale.

INTRODUCTION

Despite a century has passed since panic symptoms were first described, panic disorder (PD) was classified as a separate disorder entity in 1980s. According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), PD is characterized by recurrent unexpected occurrence of panic attacks (PA), followed by persistent concern about additional attacks and their consequences or a significant change in behavior as a result

of the attacks [1-3]. The epidemiological survey of PA and PD evaluation reported that lifetime prevalence estimates were 22.7% for isolated panic without agoraphobia (AG) (PA-only), 0.8% for PA with agoraphobia without PD (PA-AG), 3.7% for PD without AG (PD-only), and 1.1% for PD with AG (PD-AG) [4]. The median age of PD onset is 24 years and twice as many women suffer from it compared to men [1,2]. Moreover, PD patients are prone to comorbid diseases. The lifetime prevalence of major depressive disorders (MDDs) increases up to 50 to 60% and these patients are characterized by poorer psychopathologies and higher level of suicidality [5].

Family and twin studies reveal a genetic contribution to the pathogenesis of PD with an average heritability of up to 48% [3]. Defining the susceptibility genes for PD has not been an easy step though some positive associations

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Address for correspondence: Zeynep Yegin

Medical Laboratory Techniques Program, Vocational School of Health Services, Sinop University, Sinop 57000, Turkey

E-mail: zyegin1@gmail.com

ORCID: <https://orcid.org/0000-0003-4637-0253>

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have been clarified. These associations imply genes encoding serotonin receptors/transporters, cholecystokinin receptors, neurotransmitter degradation enzymes, regulators of G protein signaling, and molecules involved in neuronal growth/differentiation [2]. The difficulties and inconsistencies with these genetic searches necessitated somehow different molecular approaches and microRNA (miRNA) studies emerged as a result of these alternative approaches in psychiatry field. miRNAs are small, approximately 22-nucleotide noncoding RNA molecules that play a significant role in the transcriptional and post-transcriptional regulations of gene expression via binding to the 3' untranslated regions (UTRs) of target mRNAs. They regulate the stability and translation of up to 60% of protein-coding mRNAs [6-8]. It has been reported that more than half of the miRNAs identified are upregulated in the brain, where they display important roles as regulators of neuronal genes which are responsible of the function, plasticity and development of the brain [9-11]. Because of their significant roles in affecting neuronal and circuit formation as regulator molecules, miRNAs and their regulatory networks have been accepted as promising candidates in genetic liability to multiple neurodegenerative and psychiatric disorders [11,12].

Several miRNA risk variants were characterized in psychiatric disorders; miR-30e rs178077483 in MDD [6], miR-30e rs112439044 in schizophrenia [13], miR138-2 rs139365823 in schizophrenia [14], miR-206 rs16882131 in bipolar I disorder [8], miR-708 rs754333774 in bipolar disorder and schizophrenia [15], miR-34c rs2187473 in MDD [16], miR-143 rs4705342 and rs4705343 in schizophrenia [12], miR-137 rs1625579 in bipolar disorder [17]. Among the miRNA variations studied in psychiatric disorders up to now, miR-137 gene has strikingly become prominent and gained a great significance in schizophrenia both in terms of susceptibility to the disease onset and effects on several clinical aspects such as cognitive functioning, gray matter structure and cortical morphology [7,11,18-21]. New promising miRNA candidates are also necessitated for PD. miR-155 and miR-22 were targeted in the study because of their possible roles in neurological and psychiatric disease mechanisms. Our study is quite innovative in terms of combined design of these promising miRNAs in PD. This is the first survey of miR-155 rs767649 variant in PD. Besides, possible association of miR-22 rs8076112 with PD was only investigated in

Korean population [3] and no other study has been reported.

With the purpose of characterizing promising miRNA gene risk variants in PD, we evaluated miR-22 rs8076112 and miR-155 rs767649 in a cohort of PD patients and healthy controls. To evaluate PD phenotypes, the Panic Disorder Severity Scale (PDSS) was also administered to patients and the possible associations between the scale and risk variants were also analyzed.

METHODS

Subjects and Clinical Assessments

The present case-control investigation was conducted between December 2020 and October 2023. The study sample consisted of 134 patients with PD recruited at the Department of Psychiatry, Faculty of Medicine, Ondokuz Mayıs University according to the diagnostic criteria provided in DSM-V. Patients with a history of any other psychiatric disorder, mental retardation and subjects who were unwilling to participate were excluded. Also, 140 healthy controls comprising university staff and students without a personal or family history of psychiatric disorders among first-degree relatives were included in the study. Both patient and control subjects were of Turkish descent.

To evaluate clinical severity of the disease, Turkish validated version [22] of PDSS [23] was administered to all subjects. The Turkish validated version of PDSS was reported to have high sensitivity (99%) and specificity (98%) [22]. The PDSS is a seven-item, interview-based scale for assessing the severity of PD. This scale comprises five items assessing PA and associated symptoms including frequency of PA, distress during PA, anticipatory anxiety, agoraphobic fear and avoidance, and interoceptive fear and avoidance. Two other items of the scale evaluate work functioning and social impairment. On the basis of the patient's responses, the severity of each feature is rated between 0 (none) and 4 (the highest) and thus total score is recorded between ranges of 0 to 28 [23]. Further demographic and clinical details such as age, sex, level of education, onset age, average years of disease, etc. were recorded for each patient.

The study was approved by the Medical Ethics Committee of Ondokuz Mayıs University (OMU KAEC 2020/709). All study procedures complied with Institutional Review

Board regulations, the Declaration of Helsinki, and the principles of Good Clinical Practice. All participants gave oral and written consent after receiving the description of the study.

Genotyping Protocols

Peripheral blood samples were collected in EDTA containing tubes to be used in DNA isolation procedures. DNA extractions were performed with PureLink™ Genomic DNA Mini Kit (Invitrogen-Thermo Fisher Scientific) and the extracted DNA samples were stored at -20°C for further genotyping analyses. Genotyping analyses were made with polymerase chain reaction-restriction fragment length polymorphism method previously reported in the literature [3,24]. Primer sequences for miR-155 rs767649: F: 5'-CCT GTA TGA CAA GGT TGT GTT TG-3' R: 5'-GCT GGC ATA CTA TTC TAC CCA TAA-3' and miR-22 rs8076112: F: 5'-CCC CCT TCT CAG AAA AGC TC-3' and R: 5'-CAG CTG GGG AGT CCA GAT AC-3'. Polymerase chain reaction (PCR) was carried out in a 25 μl mixture containing 1 $\times$ Taq buffer, 2 mM MgCl_2 , 0.2 mM dNTP, 0.5 μM of forward and reverse primer pair, 1.5 U Taq DNA polymerase (Thermo Fisher Scientific) and ~ 200 ng of DNA sample. Thermal cycler conditions for miR-155 rs767649 were as follows: 35 cycles of 40 seconds at 94°C ; annealing for 45 seconds at 60°C ; and extension for 45 seconds at 72°C . A predenaturation step for 6 minutes at 94°C and a final extension step for 12 minutes at 72°C were included. miR-22 rs8076112 thermal cycler conditions were the same except the annealing temperature (63°C). Amplicons were controlled on 2.5% agarose gel stained with ethidium bromide by electrophoresis and analyzed with transilluminator device to confirm the expected amplicon sizes of 293 bp and 178 bp for miR-155 rs767649 and miR-22 rs8076112, respectively. For the analysis of miR-155 rs767649 genotypes, amplified fragments were digested with Tsp45I restriction enzyme (Thermo Fisher Scientific) at 37°C for 2 h and were separated by electrophoresis. The unrestricted PCR product (AA genotype) had a size of 293 bp; complete restriction (TT genotype) produced bands of 157 bp and 136 bp. Heterozygotes had all the bands. For the analysis of miR-22 rs8076112, the digestion of the amplicons with Styl restriction enzyme (Thermo Fisher Scientific) at 37°C for 2 h resulted in AA: 178 bp; CC: 97 bp and 81 bp; AC: 178 bp, 97 bp, 81 bp fragments.

Statistical Analyses

Statistical analyses were conducted using the IBM SPSS Statistics 25 software package. To present clinical and demographic data, we utilized the number of observations, percent, and mean $\pm$ standard deviation. We compared quantitative data between groups through the Kruskal-Wallis test while qualitative variables were analyzed using the Fisher exact test. Additionally, logistic regression analysis was conducted to examine the impact of miR-155 rs767649 and miR-22 rs8076112 polymorphism genotypes on the likelihood of developing PD. Statistical tests were subjected to significance control at a level of 0.05.

RESULTS

Demographic and Clinical Characteristics of the Study Participants

The demographic and clinical data of the patients and control group are presented in Tables 1 and 2. The patient group consisted of 58.96% women and 41.04% men while the ratios of the participants in the control group were 60.71% women and 39.29% men. The mean ages of the patients and controls were 36.34 ± 11.53 and 39.14 ± 9.50 , respectively. The mean age of onset for patients with PD was 27.49 ± 10.38 and the mean age of treatment onset was 30.25 ± 10.38 . The mean treatment duration (months) was 16.50 ± 35.09 . The mean for PDSS was determined as 14.51 ± 5.51 (Tables 1, 2).

Genotype and Allele Distributions of the miRNA Variations

Genotypes and allele distributions of the analyzed variants in patients with PD and controls are presented in Table 3. The genotypes and frequencies of miR-155 rs767649 and miR-22 rs8076112 single nucleotide polymorphisms (SNPs) were found in Hardy-Weinberg equilibrium (HWE) at $p < 0.05$ significance level. Logistic regression analysis was conducted to evaluate the possible impacts of miR-155 rs767649 and miR-22 rs8076112 variants to confer susceptibility to PD. According to the results, there was no difference for miR-155 rs767649 genotypes/alleles between patients and controls. However, there was a statistically significant association for miR-22 rs8076112 genotypes/alleles between patients and controls. miR-22 rs8076112 CC genotypes were lower in patients compared to controls (1.5% versus 6.4%, $p =$

Table 1. Demographic and clinical data of categorical variables

Group		Cases	Controls
Gender	Woman	79 (58.96)	85 (60.71)
	Man	55 (41.04)	55 (39.29)
Marital status	Married	78 (58.21)	-
	Single	56 (41.79)	-
Employment status	Yes	96 (71.64)	-
	No	38 (28.36)	-
Place of residence	Village/town	17 (12.69)	-
	City	117 (87.31)	-
Socioeconomic status	Low	22 (16.42)	-
	Middle/high	112 (83.58)	-
Nocturnal panic	Absent	78 (58.21)	-
	Present	56 (41.79)	-
Triggering/associated first event before disease	Absent	45 (34.33)	-
	Present	89 (65.67)	-
If yes, triggering/associated first event	Death of a close person	21 (15.67)	-
	Life-threatening event	34 (25.37)	-
	Psychosocial stress factor	34 (25.37)	-
Object carrying	Absent	73 (54.48)	-
	Present	61 (45.52)	-
Psychiatric disorder in first-degree relatives	Absent	72 (53.73)	-
	Panic disorder	45 (33.58)	-
	Other	17 (12.69)	-
Panic Disorder Severity Scale score ≥ 7	Absent	12 (8.96)	-
	Present	122 (91.04)	-

Values are presented as number (%).

-, not available.

Table 2. Quantitative demographic and clinical data

Variables	Patients				Controls			
	N	Mean	SD	Median	N	Mean	SD	Median
Age (yr)	134	36.34	11.53	37.50	140	39.14	9.50	38.00
Education (yr)	134	12.48	3.43	12.00		-		
Child	134	1.22	1.17	1.00		-		
Disease onset (yr)	134	27.49	10.38	25.00		-		
Treatment onset (yr)	134	30.25	10.38	29.00		-		
Treatment duration (mo)	134	16.50	35.09	6.00		-		
Panic Disorder Severity Scale	134	14.51	5.51	14.00		-		

SD, standard deviation; -, not available.

0.041). Logistic regression analysis proved the highly protective effect (80.4%) of CC genotype against PD ($p = 0.041$, odds ratio = 0.196, 95% confidence interval = 0.041–0.934) (Table 3, Fig. 1).

Correlation of miRNA Genotypes with Clinical Findings and Disease Severity

The possible associations between categorical and quantitative variables (Tables 1, 2) and miR-155 rs767649 were analyzed with Fisher's exact and Kruskal-Wallis tests, respectively. A statistically significant association

was not found ($p > 0.05$).

The possible associations between categorical and quantitative variables and miR-22 rs8076112 were also analyzed with Fisher's exact and Kruskal-Wallis tests, respectively. A statistically significant association was not found ($p > 0.05$).

Two different approaches analyzed the possible association of the investigated miRNA variants with PDSS. PDSS scores of the patients were grouped as absent and present according to the cut-off value ≥ 7 used in the literature [22] and the relationship with miR-155 rs767649 and

Table 3. Genotype and allele distributions of miR-155 rs767649 and miR-22 rs8076112 in patients with PD and controls

Genotype	Cases	Controls	<i>p</i> value	OR (95% CI)
miR-155 rs767649				
AA	3 (2.2)	5 (3.6)		
AT	23 (17.2)	29 (20.7)	0.721	1.322 (0.286–6.119)
TT	108 (80.6)	106 (75.7)	0.476	1.698 (0.396–7.284)
A allele frequency	29 (0.108)	39 (0.139)	0.301	
T allele frequency	239 (0.892)	241 (0.861)		
miR-22 rs8076112				
AA	94 (70.1)	83 (59.3)		
AC	38 (28.4)	48 (34.3)	0.175	0.699 (0.416–1.173)
CC	2 (1.5)	9 (6.4)	0.041*	0.196 (0.041–0.934)
A allele frequency	226 (0.843)	214 (0.764)	0.024*	
C allele frequency	42 (0.157)	66 (0.236)		

Values are presented as number (%).

miR-155, microRNA-155; miR-22, microRNA-22; PD, panic disorder; OR, odds ratio; CI, confidence interval.

* $p < 0.05$.

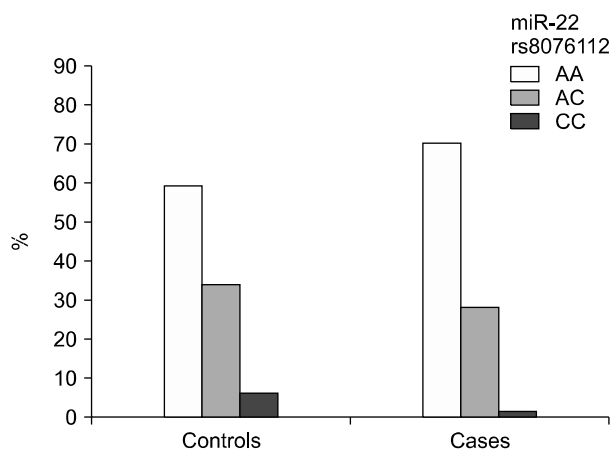


Fig. 1. Protective effect of miR-22 rs8076112 CC genotype against panic disorder.
miR-22, microRNA-22.

miR-22 rs8076112 genotypes was analyzed with Fisher Exact test. As a result of the test statistics, no significant relationship was found between PD status and the investigated genotypes of the patients ($p > 0.05$). Besides, the medians of the PDSS scores of patients with miR-155 rs767649 and miR-22 rs8076112 genotypes were also compared with the Kruskal-Wallis test. It was determined that the PDSS medians did not show a statistically significant difference in patients with different genotypes ($p > 0.05$). miR-155 rs767649 and PDSS association: The scores for PDSS were 13 ± 9.17 , 16.04 ± 4.45 and 14.23 ± 5.61 for AA, AT and TT genotypes, respectively (K-W: 2.54, $p = 0.281$). miR-22 rs8076112 and PDSS association: The scores for PDSS were 14.46 ± 5.58 , $14.87 \pm$

5.37 and 10.5 ± 6.36 for AA, AC and CC genotypes, respectively (K-W: 0.85, $p = 0.652$).

DISCUSSION

miR-155 is an important member of miRNAs and display crucial roles in organism such as differentiation of hematopoietic cells, immunization, inflammation and cardiovascular diseases. miR-155 mediated the inflammatory injury in hippocampal neuronal cells via activating the microglial cells [25]. Downregulated expression of intracellular miR-155 together with let-7e and miR-146a as regulators of toll-like receptor (TLR) signaling was shown in peripheral blood mononuclear cells (PBMCs) of MDD patients. Upregulation of the genes was reported after antidepressant therapy for four weeks [26]. In depression model mice it was shown that the expression level of miR-155 could reduce the release of inflammatory factors and the apoptosis of hippocampal neurons and thus improve depression-like behavior [27]. Besides its significance in the inflammatory response, miR-155 would also play a role in expression of circadian clock gene BMAL1 mRNA and protein levels. In the analysis of fifteen miRNAs in plasmas of bipolar disorder patients, decreased expression levels of miR-155 and miR-15b were shown in the patient group compared to the controls [28]. The above summarized studies may refer to the significance of miR-155 in psychiatric disorders. Besides, the functionality of rs767649 SNP in the promoter of miR-155 was demonstrated in a cervical cancer study; luciferase

assay indicated that the transition of A to T allele could lead to miR-155 downregulation at the transcriptional level [29]. Our study did not reveal an association between functional rs767649 variant and PD susceptibility and disease severity. Since this is the first survey of miR-155 rs767649 variant in PD, further replication studies are highly recommended.

In a very comprehensive study for 712 SNPs tagging 325 human miRNA regions in a Spanish population, six SNPs were found to be associated with PD. Two SNPs (miR-22 rs6502892, miR-339 rs11763020) were associated with disease susceptibility and some other SNPs tagging miR-138-2, miR-488, miR-491 and miR-148a were associated with disease phenotypes. To functionally assess the spectrum of genes regulated by the associated miRNAs, reporter-gene assays and miRNA overexpression experiments were also conducted in neuroblastoma cells. The results showed that miR-22 regulated four genes (BDNF, HTR2C, MAOA, RGS2) which strongly refer to physiological pathways related to anxiety [2]. Aberrantly expressed miRNAs were analyzed in peripheral blood of schizophrenia patients and miR-22-3p, miR-92a-3p and miR-137 were identified by binary regression analysis. Bioinformatic and gene ontology enrichment approaches to the combination of these miRNAs revealed their strong association with synaptic structure and function [30]. The first report showing association of miR-22 rs8076112 with PD was evaluated in a Korean population [3] and no other study has existed thereafter. The authors reported significant associations of PD with miR-22 8076112 genotype, miR-22 rs8076112C/rs6502892C haplotype, and the combination of miR-22 rs8076112AC/rs6502892CC or rs8076112CC/rs6502892CC. Our results differ from this study since we put forward the protective effect of miR-22 rs8076112 CC genotype against PD (Table 3, Fig. 1). Further studies in different populations are warranted.

In conclusion, we analyzed miR-155 rs767649 and miR-22 rs8076112 as candidate genetic variants for PD susceptibility by performing a genetic association study. The possible association of the variants with disease severity was assessed with PDSS. Though miR-155 rs767649 did not provide evidence for disease, miR-22 rs8076112 was significantly associated with PD; logistic regression analysis proved the highly protective effect (80.4%) of CC genotype against the disease. There was no association between the variants and PDSS. To the best of our knowl-

edge, this is the first study evaluating the effects of miR-155 rs767649 and miR-22 rs8076112 variants together in terms of both PD susceptibility and disease severity. The limitation of our study is relatively small number of the participants stemming from the recruitment of the patients from a single center. Both patient and control subjects were of Turkish descent. Further studies which have larger samples from other ethnic populations are needed to fully clarify the role of the analyzed miRNA variants in PD.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Zeynep Yegin, Gokhan Sarisoy. Methodology: Zeynep Yegin, Gokhan Sarisoy, Ahmet Uzun, Haydar Koc. Investigation: Zeynep Yegin, Gokhan Sarisoy, Ahmet Uzun, Haydar Koc. Project administration: Haydar Koc. Funding: Haydar Koc. Writing—original draft: Zeynep Yegin. Writing—review & editing: Gokhan Sarisoy, Ahmet Uzun, Haydar Koc. All authors have read and approved the final manuscript.

■ ORCID

Zeynep Yegin	https://orcid.org/0000-0003-4637-0253
Gokhan Sarisoy	https://orcid.org/0000-0003-0050-8157
Ahmet Uzun	https://orcid.org/0009-0006-7539-5598
Haydar Koc	https://orcid.org/0000-0002-8568-4717

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