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Association Between Sirtuin 1 (SIRT1) Gene Polymorphisms and Suicide Attempts in Schizophrenia: An Exploratory Study

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ABSTRACT

Objective: Schizophrenia is a neuropsychiatric disorder with a high risk of suicide, arising from the interplay between genetic predisposition and environmental factors. The Sirtuin 1 (SIRT1) gene, an NAD^+-dependent deacetylase, is involved in cellular stress response, apoptosis, and mitochondrial functions, as well as neuroprotection and circadian rhythm regulation. SIRT1 is thought to influence neurobiological mechanisms related to cognitive and affective regulation. This study aimed to investigate the association between specific SIRT1 gene polymorphisms and suicide attempts in patients with schizophrenia.

Methods: This cross-sectional, observational genetic association study included only a case group comprising 100 patients diagnosed with schizophrenia. Targeted sequencing of the SIRT1 gene, encompassing all coding exons and their exon-intron junctions, was performed. Based on minor allele frequency and technical quality criteria, 10 single nucleotide polymorphisms (SNPs) were selected for further analysis. Linkage disequilibrium (LD) assessment, haplotype structure, and genetic modeling were conducted using the SHEsis software platform.

Results: The rs10997870 GG genotype (p=0.017) and the rs7896005 AA genotype (p=0.033) were associated with suicide attempts, whereas the rs2236318 A allele (p=0.015) and the rs41299232 GG genotype (p=0.027) were found to be protective. The C-T-A-G haplotype (p=0.005) was associated with an increased risk, while the G-A-G-T haplotype (p=0.032) showed a protective effect.

Conclusion: Certain polymorphisms and haplotypes within the SIRT1 gene may be associated with suicide risk among patients with schizophrenia. These findings point to the potential role of genetic profiling in identifying high-risk individuals. Further large-scale studies are warranted to increase the generalizability of the findings and to elucidate the underlying mechanisms in greater detail.

Keywords: Haplotypes, schizophrenia, single nucleotide polymorphism, sirtuins, suicide attempt

INTRODUCTION

Schizophrenia is a chronic psychiatric disorder characterized by progressive cognitive impairment and disturbances in affective regulation, leading to substantial functional disability (Jauhar et al. 2022). Despite advances in treatment, the life expectancy of patients with schizophrenia is reduced by approximately 10–25 years, with suicide being one of the leading causes of premature death (Correll et al. 2022). Genetic predisposition, in combination with environmental stressors, plays a significant role in the etiology of both schizophrenia and suicidal behavior (Sudol and Mann, 2017; Wahbeh and Avramopoulos, 2021).

Recent studies have highlighted the role of gene–environment interactions and complex polygenic inheritance in the development of schizophrenia (Wahbeh and Avramopoulos, 2021; Rantala et al. 2022). In particular, genes associated with neuroinflammation, neurodevelopment, and synaptic

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plasticity —such as BDNF, SLC39A8, and those regulating circadian rhythms— have garnered considerable research interest (Milhiet et al. 2011; Fang et al. 2019; Rantala et al. 2022; Ahmad et al. 2023). Among these, Sirtuin 1 (SIRT1) has garnered increasing attention due to its dual role in neuroprotection and circadian rhythm regulation (Asher et al. 2008; Chang and Guarente, 2013).

SIRT1 encodes an NAD^+-dependent deacetylase that modulates numerous cellular processes, including oxidative stress response, apoptosis, and mitochondrial function (Wu et al. 2022). It also regulates core circadian genes such as BMAL1, PER2, and CRY1, thereby directly influencing cognitive and affective processes (Asher et al. 2008; Belden and Dunlap, 2008; Nakahata et al. 2009). Disruption of the circadian system has been linked to schizophrenia, particularly in the context of sleep disturbances and mood fluctuations (Aftanas et al. 2018; Fang et al. 2019; Kishi et al. 2010, 2011).

Findings regarding the behavioral effects of SIRT1 is also accumulating. In animal models, SIRT1 activation in the prefrontal cortex and hippocampus has been shown to reduce inflammatory responses and attenuate depressive-like behaviors (Hurley et al. 2014; Abe-Higuchi et al. 2016; Niu et al. 2020). At the genetic level, SIRT1 polymorphisms have been associated with various psychiatric phenotypes, including major depressive disorder, bipolar disorder, and suicidal behavior (Kishi et al. 2010, 2011). For example, the rs2236318 TT, rs36107781 TC, and rs7896005 AA genotypes have been linked to depressive symptoms, while the rs10997870 GG genotype has been associated with suicidal behavior in bipolar disorder (Kishi et al. 2010; Nivoli et al. 2016).

SIRT1 variants may be associated not only with mood regulation but also with personality traits such as aggression and antisocial behavior. The rs4746720 CC genotype has been inversely associated with impulsive behaviors during adolescence (Chang et al. 2017). Furthermore, significant associations have been reported between SIRT1 genotypes and depressive symptoms in patients with schizophrenia, alongside decreased plasma SIRT1 levels (Fang et al. 2019; Wang et al. 2020).

In light of this evidence, the present study aimed to investigate the relationship between certain SIRT1 gene polymorphisms and suicide attempts in a sample of patients with schizophrenia from Türkiye. By identifying genetic variants associated with suicidal behavior, we sought to contribute to the field of personalized psychiatry and provide novel perspectives for the development of effective suicide prevention strategies in this vulnerable patient group.

METHODS

Participants

This study was a cross-sectional, observational genetic association investigation including only a case group. Clinical records of the participants were retrospectively reviewed, and blood samples for genetic analysis were obtained after informed consent was secured. The study sample was established from patients with schizophrenia receiving follow-up care at the Psychosis Outpatient Clinic of a university hospital in Türkiye.

A total of 281 patients who were diagnosed with schizophrenia according to the DSM-5 criteria, aged between 18 and 65 years, literate, in remission under pharmacological treatment, and receiving outpatient care, were initially evaluated. Only those with clinical documentation confirming at least one lifetime suicide attempt, or explicitly confirming no history of suicide attempts, were eligible for inclusion. Individuals were excluded if they had intellectual disability, bipolar disorder with psychotic features (mania or depression), schizoaffective disorder, delusional disorder, autism spectrum disorder, pregnancy or lactation, a known history of genetic disorders, or incomplete clinical/sociodemographic data. In addition, patients who provided insufficient blood samples (n=14) or declined participation due to the COVID-19 pandemic (n=36) were excluded.

Sample size estimation was performed using G*Power version 3.1. Based on the standard medium effect size commonly reported in the literature (Cohen's d=0.5), with 80% statistical power and a significance level of 5%, a minimum of 64 participants per group was determined to be necessary. However, as the study period coincided with the COVID-19 pandemic, recruitment rates were reduced and some patients could not be included, resulting in a final sample size smaller than the target.

Ultimately, 100 patients meeting all eligibility criteria were included in the final analysis (Figure 1). Participants were classified into two groups according to their history of suicide attempts: Suicide Attempt group (SA; n=23) and No Suicide Attempt group (NSA; n=77).

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Selçuk University Faculty of Medicine (Approval No. 2020/309, Date: 10/07/2020). Written informed consent was obtained from all participants.

Clinical Assessment

Sociodemographic characteristics, clinical history, treatment records, and data on suicide attempts were obtained from routinely used psychiatric assessment forms administered at the Psychosis Outpatient Clinic.

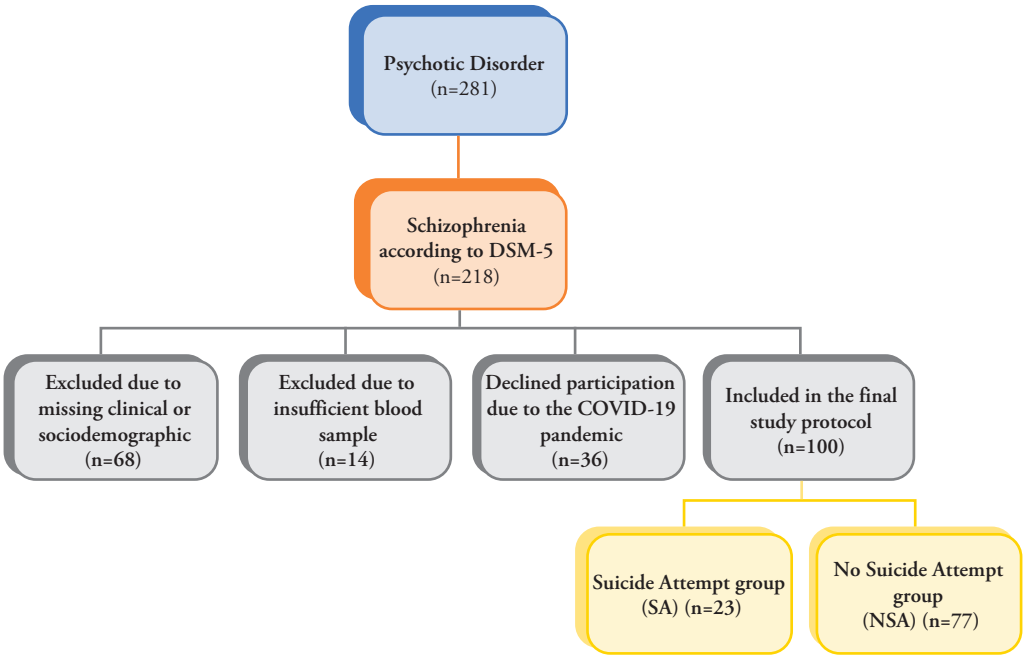

Figure 1. Flowchart showing the process of inclusion in the study

SIRT1 Gene Analysis

Genomic DNA was isolated using the DETAGEN GeneStructure Genomic Isolation Kit (Catalog No: E003.50, Lot No: 271220, Türkiye). The concentration and purity of the isolated DNA were measured with a Nanodrop Lite spectrophotometer (Thermo Scientific, USA); only samples with an A260/280 ratio between 1.80 and 2.00 were included in the study. Custom primers targeting the nine coding exons (E1–E9) and exon–intron junctions of the SIRT1 gene were designed using NCBI Primer-BLAST (Supplement 1; Table 1), based on the human reference genome (GRCh38). Primers were synthesized by Detagen and optimized according to bioinformatic criteria including GC content, melting temperature (Tm), and secondary structure formation (dimers, hairpins).

PCR amplifications were performed using the DTG *SIRT1* RT Kit (Catalog No: R052.100, Lot No: 17022021RT and 04082021RT, Türkiye). DNA quantification was performed using the Qubit 4 Fluorometer (Invitrogen, Thermo Fisher Scientific, USA) in accordance with the Qubit dsDNA BR Assay Kit protocol. Library preparation was conducted with the Nextera XT DNA Library Prep Kit (Illumina, USA). Sequencing was carried out on the Illumina iSeq 100 platform using paired-end reads (2×150 bp).

Post-sequencing quality control was performed using FASTQC v0.11.9. Raw data were obtained in FASTQ format, and appropriate bioinformatic pipelines for alignment and variant calling were applied.

Statistical Analysis

Statistical analyses were conducted using IBM Statistical Package for Social Sciences (SPSS) program version 25. The Shapiro-Wilk test was used to assess the normality of continuous variables. Non-normally distributed variables were analyzed with non-parametric tests such as the Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate, and odds ratios (OR) with 95% confidence intervals (CI) were calculated. Hardy-Weinberg equilibrium was assessed using the chi-square test.

For multiple SNP comparisons, false discovery rate (FDR) correction based on the Benjamini-Hochberg method (FDR_BH) was applied to control for type I error. Haplotype structure and linkage disequilibrium (LD) analyses were performed using the SHEsis software platform (Shi and He, 2005; Li et al. 2009; Shen et al. 2016). Genetic association analyses were conducted under codominant, dominant, recessive, and overdominant models. A p-value <0.05 was considered statistically significant for all analyses.

RESULTS

Sociodemographic and Clinical Characteristics

The sociodemographic and clinical characteristics of the participants are summarized in Table 1. A total of 100 patients were included in the analysis; of these, 77 (77%) were in the No Suicide Attempt (NSA) group and 23 (23%)

were in the Suicide Attempt (SA) group, defined as having at least one documented lifetime suicide attempt. Overall, 60% of participants were male and 40% were female; 64% were single or divorced, and 71% were unemployed. The mean age of the participants was 38.4±9.2 years. Approximately 70% of participants reported no family history of psychiatric disorders, 40% were current smokers, and 3% reported alcohol or substance use.

Regarding clinical characteristics, approximately 70% of participants had no history of antidepressant treatment, and the onset of the disorder was most commonly characterized by positive symptoms such as delusions or hallucinations. Patients in the SA group exhibited a younger age at onset and a shorter duration of untreated psychosis compared to the NSA group; however, these differences were not statistically significant (p>0.05). Notably, the SA group had a longer duration of hospitalization, with this difference approaching marginal statistical significance (p=0.07).

Genetic Analysis

To investigate genetic factors potentially associated with suicide attempts in patients with schizophrenia, targeted sequencing was performed covering the coding exons and exon–intron junctions of the SIRT1 gene. Sequencing data identified 21 SNP variants; however, SNPs with a minor allele frequency (MAF) of less than 2% (f<0.02) were excluded, leaving a total of 10 SNPs for analysis: rs201230502, rs41299232, rs2236318, rs7896005, rs10997870, rs737477, rs2273773, rs79269275, rs36107781, and rs182199697. None of the included SNPs deviated from Hardy–Weinberg equilibrium (Supplement 2; Table 1).

As this study did not include a healthy control group, allele frequencies for the two patient groups were compared with reference values from the European population in the ALFA Project within the dbSNP database (NCBI dbSNP, 2023). Allele frequencies in the NSA group were similar to those of the reference population, whereas the SA group showed significant differences compared to both the reference and NSA groups (p<0.05), suggesting potential genetic differences associated with suicidal behavior (Supplement 2; Table 2). However, as no data were available regarding psychiatric phenotypes or ethnic background for individuals in the ALFA reference population, these comparisons should be interpreted with caution.

To minimize false-positive results from multiple SNP comparisons, false discovery rate (FDR) correction based on the Benjamini–Hochberg method (FDR_BH) was applied, and statistical significance was determined according to the adjusted values (Table 2).

Table 1. Sociodemographic and clinical characteristics of the participants

	NSA (n)/ (Mean ± SD (Min-Max))	SA (n, %)/ (Mean ± SD (Min-Max))	p
Gender			0.561[a]
Male	45 (75%)	15 (25%)	
Female	32 (80%)	8 (20%)	
Marital status			0.509[a]
Single	51 (79.7%)	13 (20.3%)	
Married	12 (66.7%)	6 (33.3%)	
Divorced	14 (77.8%)	4 (22.2%)	
Education			0.451[a]
Primary school	37 (80.4)	9 (19.6)	
High school	40 (74.1)	14 (25.9)	
Employment status			0.77[a]
Not working	54 (79.4%)	14 (20.6%)	
Working	13 (76.5%)	4 (23.5%)	
Retired	4 (66.7%)	2 (33.3%)	
Student	6 (66.7%)	3 (33.3%)	
Family history			0.175[a]
No	58 (80.6%)	14 (19.4%)	
Yes	19 (67.9%)	9 (32.1%)	
Smoking			0.783[a]
No	46 (78%)	13 (22%)	
Yes	31 (75.6%)	10 (24.4%)	
Alcohol			-
No	74 (77.1%)	22 (22.9%)	
Yes	3 (75%)	1 (25%)	
Drug use			-
No	75 (77.3%)	22 (22.7%)	
Yes	2 (66.7%)	1 (33.3%)	
Onset symptoms			0.616[a]
Negative	24 (80%)	6 (20%)	
Positive	50 (76.9%)	15 (23.1%)	
Other	3 (60%)	2 (40%)	
Antidepressant use			0.10[a]
No	60 (81.1%)	14 (18.9%)	
Yes	17 (65.4%)	9 (34.6%)	
Education (y)	9.41±4.63 (0–21)	10.4±4.75 (5–21)	0.464[b]
Number of children	0.71±1.25 (0–5)	0.86±1.10 (0–3)	0.232[b]
First negative s. (a)	22.67±8.30 (13–63)	21.8±6.95 (1–40)	0.485[b]
First positive s. (a)	23.84±8.28 (13–63)	22.3±7.11 (12–42)	0.276[b]
Disease onset (a)	24.22±8.34 (15–63)	22.8±6.75 (16–42)	0.342[b]
DUP (y)	1.635±2.52 (0.04–15.4)	1.24±1.57 (0.02–7.7)	0.586[b]
Hospitalization (n)	3.42±3.29 (0–15)	4.4±2.80 (0–10)	0.07[b]

n: number, SA: suicide attempt, NSA: non-suicide attempt, Y: year, a: Age, DUP: duration of untreated psychosis, D: duration, S: symptom, SD: standard deviation, Min: minimum, Max: maximum, [a]Chi-square Test, [b]: Mann-Whitney U Test.

Table 2. Genotype and allele distribution of SNPs

Genetic model	Genotype	NSA (n=77) (n (%))	SA (n=23) (n (%))	OR (95% CI)	χ^2	Pp	Fp	FDR BH
[b]**rs201230502**					4.068	0.043*	0.078	0.07
—	T/T	75 (97.4%)	20 (87%)	1.00				
	T/C	2 (2.6%)	3 (13%)	5.62 (0.88–35.99)				
**Allele	T	152 (99%)	43 (93%)	5.30 (0.86–32.75)	3.964	0.046*	0.08	
	C	2 (1%)	3 (7%)					
[b]**rs41299232**					7.187	0.027*	0.023*	0.03*
Codominant	C/C	16 (20.8%)	10 (43.5%)	1.00		0.018*		
	C/G	42 (54.5%)	12 (52.2%)	0.46 (0.17–1.26)				
	G/G	19 (24.7%)	1 (4.3%)	0.08 (0.01–0.73)				
Dominant	C/C	16 (20.8%)	10 (43.5%)	1.00		0.036*		
	C/G-G/G	61 (79.2%)	13 (56.5%)	0.34 (0.13–0.92)				
Recessive	C/C-C/G	58 (75.3%)	22 (95.7%)	1.00		0.016*		
	G/G	19 (24.7%)	1 (4.3%)	0.14 (0.02–1.10)				
Overdominant	C/C-G/G	35 (45.5%)	11 (47.8%)	1.00		0.84		
	C/G	42 (54.5%)	12 (52.2%)	0.91 (0.36–2.31)				
[a]Allele	C	74 (48%)	32 (70%)	2.47 (1.22–4.99)	6.58	0.01*	0.011*	
	G	80 (52%)	14 (30%)					
[b]**rs2236318**					6.765	0.033*	0.033*	0.03*
Codominant	T/T	26 (33.8%)	14 (60.9%)	1.00		0.014*		
	T/A	42 (54.5%)	9 (39.1%)	0.40 (0.15–1.05)				
	A/A	9 (11.7%)	0 (0%)	0.00 (0.00-NA)				
Dominant	T/T	26 (33.8%)	14 (60.9%)	1.00		0.021*		
	T/A-A/A	51 (66.2%)	9 (39.1%)	0.33 (0.13–0.86)				
Recessive	T/T-T/A	68 (88.3%)	23 (100%)	1.00		0.026*		
	A/A	9 (11.7%)	0 (0%)	0.00 (0.00-NA)				
Overdominant	T/T-A/A	35 (45.5%)	14 (60.9%)	1.00		0.19		
	T/A	42 (54.5%)	9 (39.1%)	0.54 (0.21–1.39)				
[a]Allele	T	94 (61%)	37 (80%)	0.38 (0.17–0.84)	5.896	0.015*	0.02*	
	A	60 (39%)	9 (20%)					
[b]**rs7896005**					6.814	0.033*	0.024*	0.03*
Codominant	A/A	18 (23.4%)	10 (43.5%)	1.00		0.017*		
	A/G	38 (49.4%)	12 (52.2%)	0.57 (0.21–1.56)				
	G/G	21 (27.3%)	1 (4.3%)	0.09 (0.01–0.74)				
Dominant	A/A	18 (23.4%)	10 (43.5%)	1.00		0.067		
	A/G-G/G	59 (76.6%)	13 (56.5%)	0.40 (0.15–1.06)				
Recessive	A/A-A/G	56 (72.7%)	22 (95.7%)	1.00		0.0085*		
	G/G	21 (27.3%)	1 (4.3%)	0.12 (0.02–0.96)				
Overdominant	A/A-G/G	39 (50.6%)	11 (47.8%)	1.00		0.81		
	A/G	38 (49.4%)	12 (52.2%)	1.12 (0.44–2.84)				
[a]Allele	A	74 (48%)	32 (70%)	2.47 (1.22–4.99)	6.58	0.01*	0.011*	
	G	80 (52%)	14 (30%)					
[b]**rs10997870**					8.042	0.017*	0.014*	0.03*
Codominant	G/G	15 (19.5%)	10 (43.5%)	1.00		0.011*		
	G/T	42 (54.5%)	12 (52.2%)	0.43 (0.15–1.20)				
	T/T	20 (26%)	1 (4.3%)	0.08 (0.01–0.65)				
Dominant	G/G	15 (19.5%)	10 (43.5%)	1.00		0.025*		
	G/T-T/T	62 (80.5%)	13 (56.5%)	0.31 (0.12–0.85)				
Recessive	G/G-G/T	57 (74%)	22 (95.7%)	1.00		0.012*		
	T/T	20 (26%)	1 (4.3%)	0.13 (0.02–1.02)				
Overdominant	G/G-T/T	35 (45.5%)	11 (47.8%)	1.00		0.84		
	G/T	42 (54.5%)	12 (52.2%)	0.91 (0.36–2.31)				
[b]Allele	G	72 (47%)	32 (70%)	2.60 (1.29–5.26)	7.384	0.006*	0.007*	
	T	82 (53%)	14 (30%)					

Table 2 continued. Genotype and allele distribution of SNPs

Genetic model	Genotype	NSA (n=77) (n (%))	SA (n=23) (n (%))	OR (95% CI)	χ2	Pp	Fp	FDR BH
[a]**rs737477**					0.364	0.833	1	1
Codominant	A/A	61 (79.2%)	19 (82.6%)	1.00		0.74		
	A/C	15 (19.5%)	4 (17.4%)	0.86 (0.25–2.89)				
	C/C	1 (1.3%)	0 (0%)	0.00 (0.00-NA)				
Dominant	A/A	61 (79.2%)	19 (82.6%)	1.00		0.72		
	A/C-C/C	16 (20.8%)	4 (17.4%)	0.80 (0.24–2.69)				
Recessive	A/A-A/C	76 (98.7%)	23 (100%)	1.00		0.47		
	C/C	1 (1.3%)	0 (0%)	0.00 (0.00-NA)				
Overdominant	A/A-C/C	62 (80.5%)	19 (82.6%)	1.00		0.82		
	A/C	15 (19.5%)	4 (17.4%)	0.87 (0.26–2.94)				
[b]Allele	A	137 (89%)	42 (91%)	0.77 (0.24–2.41)	0.206	0.649	0.788	
	C	17 (11%)	4 (9%)					
[a]**rs2273773**					0.302	0.859	1	1
Codominant	T/T	63 (81.8%)	19 (82.6%)	1.00		0.77		
	T/C	13 (16.9%)	4 (17.4%)	1.02 (0.30–3.50)				
	C/C	1 (1.3%)	0 (0%)	0.00 (0.00-NA)				
Dominant	T/T	63 (81.8%)	19 (82.6%)	1.00		0.93		
	T/C-C/C	14 (18.2%)	4 (17.4%)	0.95 (0.28–3.22)				
Recessive	T/T-T/C	76 (98.7%)	23 (100%)	1.00		0.47		
	C/C	1 (1.3%)	0 (0%)	0.00 (0.00-NA)				
Overdominant	T/T-C/C	64 (83.1%)	19 (82.6%)	1.00		0.95		
	T/C	13 (16.9%)	4 (17.4%)	1.04 (0.30–3.55)				
Allele	T	139 (90%)	42 (91%)	0.88 (0.28–2.80)	0.044	0.832	0.999	
	C	15 (10%)	4 (9%)					
[a]**rs79269275**					1.813	0.178	0.232	0.27
—	C/C	71 (92.2%)	19 (82.6%)	1.00				
	C/T	6 (7.8%)	4 (17.4%)	2.49 (0.64–9.73)				
[b]Allele	C	148 (96%)	42 (91%)	2.35 (0.63–8.71)	1.717	0.189	0.242	
	T	6 (4%)	4 (9%)					
[a]**rs36107781**					4.954	0.026*	0.047*	0.05*
—	T/T	74 (96.1%)	19 (82.6%)	1.00		0.042*		
	T/C	3 (3.9%)	4 (17.4%)	5.19 (1.07–25.20)				
[b]Allele	T	151 (98%)	42 (91%)	4.79 (1.03–22.3)	4.774	0.028*	0.05*	
	C	3 (2%)	4 (9%)					
[a]**rs182199697**					0.923	0.336	1	0.42
—	C/C	74 (96.1%)	23 (100%)	1.00				
	C/A	3 (3.9%)	0 (0%)	0.00 (0.00-NA)				
[b]Allele	C	151 (98%)	46 (100%)	NA (NA–NA)	0.909	0.34	1	
	A	3 (2%)	0 (0%)					

Single locus association test: [a]genotypes, [b]allels, SNP: single nucleotide polymorphism, SA: suicide attempt, NSA: non-suicide attempt, Pp: Pearson's p, Fp: Fisher's p, χ2:chi-square, Prp: permutation P; OR: odds ratio, CI: confidence interval *p<0.05, NA: not applicable.

Table 3. Block 1 SNPs selected for haplotype analysis: rs41299232, rs2236318, rs7896005, and rs10997870

Haplotype	SA (freq)	NSA (freq)	χ2	Fp	Pp	OR (95% CI)
CTAG	32(0.695)	71(0.461)	7.805	0.006	0.005	2.672 [1.322-5.399]
GAGT	9(0.195)	56(0.363)	4.556	0.033	0.032	0.425 [0.191-0.946]
GTGT	5(0.108)	20(0.129)	0.145	0.804	0.703	0.817 [0.288-2.312]

SA: suicide attempt, NSA: non-suicide attempt, Freq: frequency, OR: odds ratio, CI: confidence interval, Pp: Pearson's p, Fp: Fisher's p, χ2:chi-square. Global results: total NSA=77, total SA=23, Global χ2 is 6.743, Fisher's p is 0.035, Pearson's p is 0.034, Haplotypes with frequency <0.02 are ignored.

Several SNPs were found to be significantly associated with suicide attempt risk in schizophrenia:

- rs41299232:The CC genotype was associated with an increased risk of suicide attempts, whereas the GG genotype demonstrated a protective effect (p <0.05; OR=0.08, 95% CI: 0.01–0.73). In both dominant and recessive genetic models, combined CG and GG genotypes were associated with a reduced risk of suicide attempts.
- rs7896005:The AA genotype was more frequent in the SA group. In the recessive model, the GG genotype was associated with a lower risk (p=0.0085; OR=0.12, 95% CI: 0.02–0.96).
- rs10997870:The TT variant significantly reduced the risk of suicide attempts, while the GG genotype was associated with an increased risk (p <0.05; OR=2.603, 95% CI: 1.288–5.259).

Other findings:

- rs201230502:The TC genotype was more frequent in the SA group; however, due to the low frequency of the variant, the sample size was limited, and statistical significance was not retained after FDR_BH correction.
- rs2236318:The A allele was less frequent in the SA group and was significantly associated with a protective effect (p=0.015; FDR_BH=0.037; OR=0.381, 95% CI: 0.17–0.84).
- rs737477, rs2273773, rs79269275, and rs182199697:No statistically significant associations with suicide attempts were observed.

Linkage disequilibrium analysis revealed strong associations between certain SNP pairs (D'>0.8 and R^2 >0.8), particularly between rs41299232–rs7896005, rs41299232–rs10997870, and rs7896005–rs10997870. As shown in Figures 2a and 2b, LD analysis indicated the formation of a block comprising rs41299232, rs2236318, rs7896005, and rs10997870, which was subsequently included in haplotype analysis.

Haplotype analysis demonstrated that the C-T-A-G haplotype was significantly associated with an increased risk of suicide attempts (p <0.005; OR=2.672, 95% CI: 1.322–5.399), whereas the G-A-G-T haplotype exhibited a protective effect (p <0.05; OR=0.425, 95% CI: 0.191–0.946) (Table 3).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the association between *SIRT1* gene polymorphisms and suicide attempts in patients with schizophrenia in a sample from Türkiye. Our findings revealed significant associations between four *SIRT1* variants —rs41299232, rs2236318, rs7896005, and rs10997870— and suicide attempts. Specifically, the CC genotype of rs41299232, the AA genotype of rs7896005, and the GG genotype of rs10997870 were more frequently observed in individuals with a history of suicide attempts, suggesting that these variants may be associated with increased risk. In contrast, the GG genotype of rs41299232, the GG genotype of rs7896005, and the T/A–A/A genotypes of rs2236318 were observed less frequently, indicating a potential protective effect. Although the TC genotype of rs201230502 was more frequently observed in the suicide attempt group, the association did not remain statistically significant after multiple comparison correction (FDR_BH). The SNPs rs737477, rs2273773, rs79269275, and rs182199697 were not associated with suicide attempts, which may indicate that these variants have no effect or that weaker effects may have been overlooked due to the limited sample size.

In the literature, *SIRT1* variants have been shown to be associated with various psychiatric phenotypes. For example, the rs2236318 TT, rs36107781 TC, and rs7896005 AA genotypes have been associated with major depressive disorder, while the rs10997870 GG genotype has been linked to suicidal behavior in bipolar disorder (Kishi et al. 2010; Nivoli et al. 2016). *SIRT1* has been reported to be associated not only with mood disorders but also with antisocial personality traits and impulsive behaviors. Variants such as rs4746720 and the T-A-A-C haplotype have been found to be inversely related to levels of aggression and impulsivity observed during adolescence (Chang et al. 2017; Wang et al. 2022). These findings suggest that *SIRT1* may contribute to

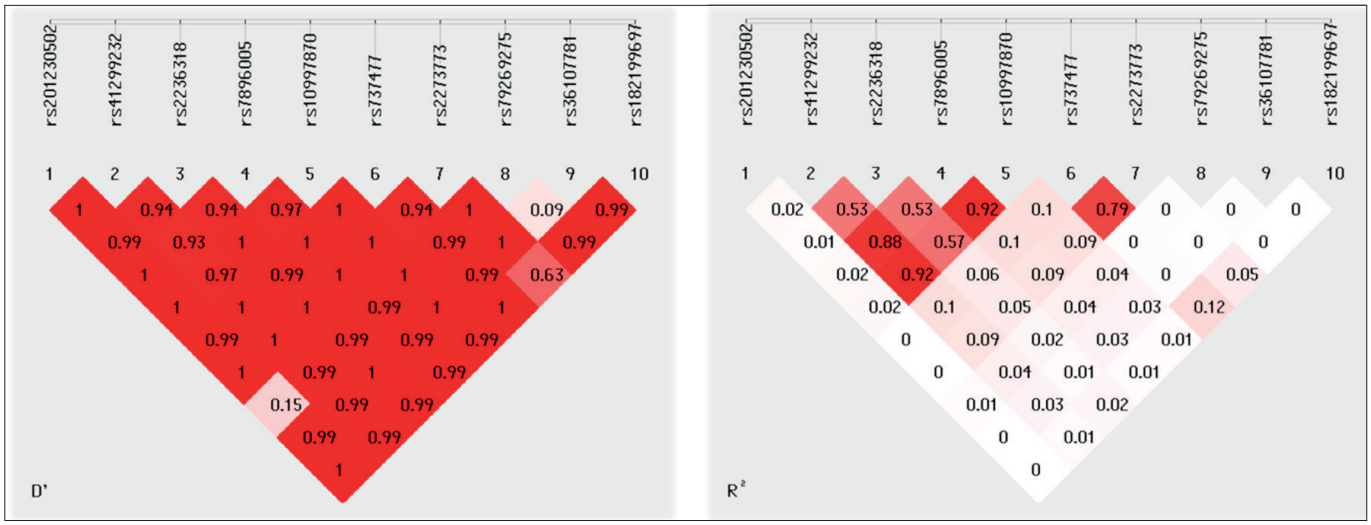

Figure 2a. Linkage Disequilibrium Analysis among Single Nucleotide Polymorphisms (SNPs) within the SIRT1 Gene
The results of the LD analysis were visualized using Lewontin's standardized coefficient (D′) values on the left and the squared Pearson correlation coefficient (R^2) values on the right. The LD plot employed conventional color schemes to illustrate the varying degrees of LD between the SNPs. Linkage disequilibrium was represented by different colors according to the following criteria: D′=0, R^2=0 indicated no LD; D′=1, R^2=1 denoted complete LD; 0.5 ≤ D′ <0.8 indicated moderate LD; and D′ >0.8 signified strong LD.

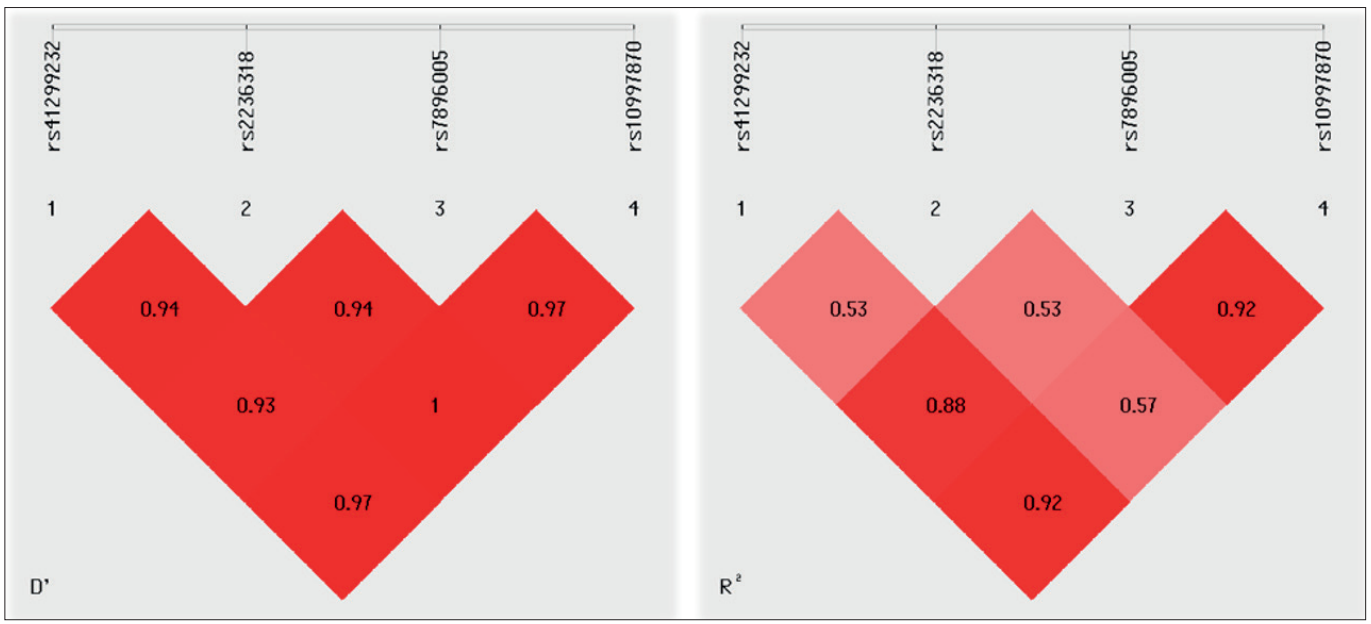

Figure 2b. Linkage Disequilibrium Analysis of the Block1 Single Nucleotide Polymorphisms (SNPs): rs41299232, rs2236318, rs7896005, rs10997870
The results of the LD analysis illustrate the genetic linkage among the four SNPs, with Lewontin's standardized coefficient (D′) values on the left and the squared Pearson correlation coefficient (R^2) values on the right. The LD plot employed conventional color schemes to depict the varying degrees of LD between the SNPs. Linkage disequilibrium was represented by different colors according to the following criteria: D′=1, R^2=1 denoted complete linkage disequilibrium; 0.5 ≤ D′ <0.8 indicated moderate LD; and D′ >0.8 signified strong LD.

suicide risk not only through mood regulation but also via behavioral phenotypes.

In our LD analysis, we identified a haplotype block comprising rs41299232, rs2236318, rs7896005, and rs10997870, in which the C-T-A-G sequence was associated with an increased risk of suicide attempts, whereas the G-A-G-T sequence was associated with protective effects. This suggests that not only individual genotypes but also specific haplotype combinations may play a role in the genetic basis of suicidal behavior.

It is known that suicidal behavior is influenced by many environmental and clinical factors in addition to genetic predisposition. In this study, some sociodemographic and clinical differences were observed between the SA and NSA groups. Although these differences were not statistically significant, higher rates of being single or divorced and unemployment in the SA group are consistent with risk factors described in the literature. Social isolation and economic stress have been reported to increase the risk of

suicide (Motillon-Toudic et al. 2022). Similarly, in patients with schizophrenia, a history of suicide attempts has been associated with unemployment, marital status, and lack of social support (Sağlam Aykut et al. 2016). Although smoking and substance use have also been associated with suicidal behavior in the literature, no statistically significant differences were observed between the two groups in this study for these variables (Sankaranarayanan et al. 2015; Esang et al. 2018).

In terms of clinical variables, the SA group tended to have an earlier age at disorder onset and a shorter duration of untreated psychosis, although these differences were not statistically significant. Another noteworthy finding was that the SA group had a longer duration of hospitalization, a difference that approached marginal significance (p=0.07) and may suggest a tendency toward more severe clinical presentations or greater treatment needs.

Although schizophrenia is often described as a neurodevelopmental disorder, increasing evidence suggesting that the disorder may also involve neurodegenerative processes could be important in explaining biological vulnerabilities in functions that influence suicidal behavior, such as emotional regulation, impulse control, and decision-making (Pino et al. 2014; Martin et al. 2015). In this context, the relationship between genes with neuroprotective functions, such as *SIRT1*, and suicide risk could be evaluated using new models that integrate both developmental and degenerative perspectives (Birnbaum and Weinberger, 2024; Sullivan et al. 2024; Sandroni and Chaumette, 2025).

From a clinical perspective, demonstrating an association between specific *SIRT1* variants and suicidal behavior provides an important starting point for genetic-based personalized psychiatric approaches. Individuals with high-risk genetic profiles could be monitored more closely, and preventive personalized interventions could be planned. Moreover, it has been suggested that mood-stabilizing effects of activators such as resveratrol, which are related to the neuroprotective effects of *SIRT1* (Albani et al. 2010; Sun et al. 2010; Hurley et al. 2014), or interventions such as light therapy aimed at regulating circadian rhythms (Alageel et al. 2018; Leite et al. 2022) may be beneficial. At the epigenetic level, the potential effects of nutrition-based interventions on mental health (Stover et al. 2018; Yan et al. 2024) are also noteworthy; however, advanced functional studies are required for such applications.

On the other hand, ethnicity was not systematically assessed in our study. Although the sample consisted of individuals living in Türkiye, the high genetic diversity of the Turkish population (Kars et al. 2021) may limit the ethnic generalizability of our findings. Since the distribution of genetic variants may be associated with ethnic background, future studies should be designed with sampling strategies that account for ethnic heterogeneity.

In conclusion, this study is among the first to demonstrate an association between *SIRT1* polymorphisms and suicidal behavior in schizophrenia. The findings should be supported by larger samples, with ethnic background controlled, and evaluated through multidimensional models that consider gene–environment interactions, while also being investigated for their functional biological correlates using advanced methodologies.

CONCLUSION

In this exploratory study conducted in a sample from Türkiye, possible associations between certain polymorphisms of the *SIRT1* gene and a history of suicide attempts in patients with schizophrenia were investigated. The findings suggest that *SIRT1* gene variants may be related to genetic mechanisms that could contribute to suicidal behavior.

A better understanding of such genetic associations may provide preliminary insight for research aimed at assessing suicide risk in patients with schizophrenia. However, given the scope and sample characteristics of this study, the findings should be interpreted with caution and supported by advanced, controlled research.

Limitations

This study is an exploratory investigation focusing solely on a case group and includes certain methodological limitations. Only individuals diagnosed with schizophrenia were included, and the absence of a healthy control group for comparative analyses limits the generalizability of the genetic variants. Moreover, the different ethnic background of the reference ALFA group and the lack of information on psychiatric phenotypes such as suicidal behavior in this group necessitate caution when interpreting comparative genetic analyses. Since participants' ethnicity data were not systematically collected, the potential impact of ethnic heterogeneity within the sample on the frequencies of genetic variants could not be evaluated. This may limit the ethnic generalizability of the findings.

The retrospective nature of data collection restricted the acquisition of information on potential confounding variables such as impulsivity, childhood trauma, and dissociative symptoms. Furthermore, depressive symptomatology that a major confounding factor in suicide research was not assessed in this study, making it difficult to evaluate the effects of genetic variants on suicidal behavior in isolation. In future studies, considering *SIRT1*'s effects on the serotonergic system and circadian rhythm, it will be important to analyze

the interactions between mood symptoms, antidepressant response, and genetic variants using multivariate models.

The small number of individuals with a history of suicide attempts may have limited the statistical power between groups, potentially preventing the detection of some genetic associations at a statistically significant level. Additionally, the conditions of conducting the study during the COVID-19 pandemic hindered the achievement of the planned sample size. The effects of the variants at the mRNA or protein level were not evaluated. All participants were under long-term antipsychotic treatment, and many were also using antidepressants, which complicates controlling for the potential contribution of medication effects on behavioral outcomes.

The results should be interpreted within the context of these limitations, and more comprehensive future studies controlling for ethnic background, pharmacological effects, mood symptoms, and epigenetic mechanisms are needed to obtain more reliable and generalizable findings.

Ethics Committe Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Selçuk University Faculty of Medicine (Approval No. 2020/309, Date: 10/07/2020). Written informed consent was obtained from all participants.

Conflict of Interest: The authors declare that they have no conflicts of interest to disclose.

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Data Availability Statement: The data supporting the findings of this study are not publicly available due to containing information that could compromise the privacy of research participants. However, access to the data can be obtained upon reasonable request by contacting the corresponding author, Memduha Aydin, at memduhaaydin@gmail.com.

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SUPPLEMENTARY

https://www.turkpsikiyatri.com/upload/64_27771_EN_SUPPL.pdf

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