Clinica Chimica Acta 588 (2026) 120978

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Genetic determinants of aggression in schizophrenia: The role of *MAOA* rs1465108 and *BDNF* rs6265 polymorphisms

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ARTICLE INFO

Keywords:
Aggression
Schizophrenia
MAOA rs1465108
BDNF rs6265

ABSTRACT

Studies have reported that the prevalence of aggression is higher in individuals with schizophrenia compared to the general population. Various factors, including genetic variations, contribute to the emergence of aggression in patients with schizophrenia. Among these, the monoamine oxidase A (*MAOA*) and brain-derived neurotrophic factor (*BDNF*) genes are considered key genetic factors potentially influencing aggressive behavior in schizophrenia. This study investigated the association of *BDNF* rs6265 and *MAOA* rs1465108 polymorphisms with aggression in schizophrenia. A total of 150 patients diagnosed with schizophrenia were included in the study. The *MAOA* rs1465108 and *BDNF* rs6265 polymorphisms were analyzed using the Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR-RFLP) method. Aggression was evaluated using the Buss-Perry Aggression Questionnaire. Suicide risk, childhood trauma, and impulsivity which were related to aggression were evaluated using the Suicide Probability Scale, the Childhood Trauma Questionnaire, and the Barratt Impulsiveness Scale, respectively. Negative and positive symptoms of schizophrenia were assessed using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS), respectively. No direct genotype associations were observed between aggression and the *BDNF* rs6265 and *MAOA* rs1465108 polymorphisms. However, impulsivity, SAPS, and SANS scores were significantly associated with aggression. These findings highlight that aggression in schizophrenia is primarily shaped by environmental and clinical factors rather than by *BDNF* or *MAOA* variants.

1. Introduction

Schizophrenia is severe neuropsychiatric disorder of multifactorial and mostly uncertain etiology. It can have a significant impact on a person's emotions, thoughts, and behaviors, causing impairment in social and occupational functionality. Although the exact cause of schizophrenia has not yet been determined, a number of risk factors have been identified. Complications during pregnancy, findings on brain imaging, neurochemical factors, neurodevelopmental factors, neurological factors, genetic factors, and social factors continue to be investigated as possible causes of schizophrenia [1]. It has been observed that patients with schizophrenia are at a higher risk of developing aggression and violent behavior when compared to the general population. The rate of aggression is 3 to 4-fold higher in patients with schizophrenia compared to controls. In line with these results, patients with schizophrenia have been found to be more likely to be convicted of violent crime [2]. Aggression in patients with schizophrenia is a critical aspect of the disorder, particularly concerning issues of violence and criminal responsibility from a forensic science perspective [3].

Aggression is a complex behavior with deep evolutionary and molecular roots in the psychology of the human being. It is generally described as anger, rage, hateful, and destructive behavior, although it has many definitions in the literature. Human aggression has a complex non-genetic basis, such as changes in the ratio of testosterone to serotonin and testosterone to cortisol, and a genetic background. It has been estimated that the genetic structure is responsible for up to 50% of

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https://doi.org/10.1016/j.cca.2026.120978
Received 5 January 2026; Received in revised form 3 March 2026; Accepted 15 March 2026
Available online 22 March 2026

aggression [4]. Several genetic studies have been conducted to identify genes that play a role in aggressive behavior. Genes responsible for regulating the serotonergic and catecholaminergic systems are thought to be key to the development of aggression and violence in schizophrenia. The most extensively studied candidate genes for the association between schizophrenia and aggression are the catechol-*O*-methyltransferase (*COMT*), serotonin transporter (*SERT/SLC6A4*), brain-derived neurotrophic factor (*BDNF*), and monoamine oxidase A (*MAOA*) genes [5].

The enzyme MAOA catalyzes the oxidation of several monoamines, including serotonin, norepinephrine, and dopamine, to their corresponding aldehydes (R-CHO) [6]. Various studies have demonstrated associations between *MAOA* variations and many neuropsychiatric diseases and aggression [7]. In a Pakistani cohort, serum MAOA levels were significantly higher in schizophrenia patients carrying the rare allele of *MAOA*-30 bp μVNTR [8]. The variable number of tandem repeats (VNTR) in the promoter region has been the focus of studies of the *MAOA* gene [9]. A study in Türkiye examined the relationship between the number of repeats in the VNTR region of the *MAOA* gene and aggression in healthy men [10]. The SNP rs1465108 is located in the first intronic region of the *MAOA* gene and results in an A > G nucleotide substitution. This polymorphism was investigated together with rs1465107, with which it is in linkage disequilibrium (LD), in a haplotype study conducted in patients with ADHD. Analysis of the association between different alleles and Conners' Parents and Teachers Rating Scale (CPRS) scores revealed that the 'G' alleles of these polymorphisms significantly contribute to ADHD [11]. To our knowledge, the relationship between the *MAOA* rs1465108 polymorphism and aggression has been investigated in only one study, which involved 376 undergraduate students and did not include patients with schizophrenia [12]; therefore, this association has not been studied in schizophrenia patients.

BDNF, a member of the neurotrophin family, plays a role in several neurodevelopmental processes, including neuronal differentiation, growth, and survival. It is an important element in brain development and plasticity, regulating the proliferation and survival of neurons [13]. Studies in animal models have shown that alterations in the *BDNF* gene may play a role in the development of aggressive behavior [14]. Decreased BDNF levels in schizophrenia and their negative association with risk assessment scores suggest that BDNF-related genetic variations may influence clinical outcomes [15]. The *BDNF* gene is located on chromosome 11p13 and consists of 11 exons and 9 promoters. It spans 66,856 base pairs and encodes a secreted protein (247 amino acids) composed of monomers and heterodimers with a molecular weight of 27,818 Da [16]. The *BDNF* gene is highly polymorphic, and the rs6265 variant polymorphism results from a G196A substitution and significantly alters BDNF protein function, affecting intracellular trafficking and signaling, and has been implicated in neurodegenerative disorders [17]. To the best of our knowledge, no study has investigated the effect of genetic variations on aggressive behavior in Turkish patients with schizophrenia.

Although aggression is common in schizophrenia and is partly influenced by genetic factors, the contribution of specific *MAOA* rs1465108 and *BDNF* rs6265 polymorphisms to aggressive behavior in Turkish patients with schizophrenia remains unclear. While MAOA regulates monoaminergic neurotransmitters such as dopamine and serotonin, BDNF modulates neuronal survival and synaptic plasticity within frontolimbic circuits associated with behavioral regulation. Dysregulation in these interconnected pathways may contribute to impaired aggression control in schizophrenia. Investigating these polymorphisms both individually and jointly may provide insight into the biological underpinnings of behavior in this population. Therefore, the primary aim of this study was to evaluate the independent contribution of the *MAOA* rs1465108 and *BDNF* rs6265 polymorphisms to aggression severity, as measured by the Buss–Perry Aggression Questionnaire, in patients with schizophrenia. The secondary aim was to evaluate the potential combined (gene-gene interaction) effect of *MAOA* rs1465108 and *BDNF* rs6265 polymorphisms on aggression in the same population.

2. Materials and methods

2.1. Case selection

This study included 150 patients with schizophrenia diagnosed according to the DSM-5 criteria (45 women and 105 men) who were admitted to the Department of Psychiatry at the Faculty of Medicine, Ankara University. Inclusion criteria for patients with schizophrenia were as follows: (i) age between 18 and 65 years, (ii) completion of at least 8 years of education, (iii) absence of akathisia and extrapyramidal movement disorders, (iv) no current substance use. Patients with mental retardation, additional psychiatric disorders, extrapyramidal side effects (dystonia, Parkinsonism, akathisia, tardive dyskinesia), or neurological disorders (stroke, epilepsy, head trauma, etc.) and history of substance abuse were excluded from the study.

Clinical assessments and data of the patients were obtained by psychiatrists through structured clinical interviews. A demographic information form including age, employment status, marital status, education level, sex, living arrangements, military service status, and disciplinary penalties during military service, history of imprisonment, and probation history was completed for the participating patients by the responsible physician. In addition, a medical history form including weight, height, history of medical illnesses, comorbid psychiatric disorders, current medications, number of hospitalizations, family history of psychiatric disorders, family history of violence/imprisonment, self-harm, suicide attempts, smoking status, alcohol use, additional substance use, childhood trauma, age at onset of illness, and duration of illness was completed by the clinician during the interview.

Institutional ethics committee approval (Approval No.: I11–670-21 in 2021) was obtained for the use of human subjects. After providing sufficient information about the study, patients were asked to sign informed consent forms and complete the relevant rating scales. Blood samples were collected from the patients on a single occasion. The collection of blood samples was carried out in accordance with the principles of the Declaration of Helsinki.

Participants were also asked to complete several assessment tools, including the Buss-Perry Aggression Questionnaire, the Childhood Trauma Questionnaire, the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS), and the Barratt Impulsiveness Scale-11.

2.2. Psychological measures

Buss-Perry Aggression Questionnaire (BPAQ): BPAQ measures 4 dimensions of aggression: rage, hostility, physical and verbal aggression. The Turkish version of BPAQ was conducted by Demirtaş-Madran with high internal consistency and stability [18].

The following psychological measures included in the study were used as covariates in the analyses, as they may influence aggression; their inclusion allow us to isolate and evaluate the main effects of *MAOA* rs1465108 and *BDNF* rs6265 genotypes on aggression.

Barratt Impulsivity Scale (BIS-11): The BIS-11 is an instrument for assessing impulsive tendencies. Three subscales are attention, motor, and non-planning types of impulsivity. This scale consists of 30 items. Each item is scored from 1 to 4. The total score of the scale is positively correlated with the individual's impulsivity level. The Turkish version of BIS-11 was conducted by Güleç et al. (2008) [19].

Childhood Trauma Questionnaire (CTQ): CTQ is a self-rated scale with subscales of emotional and physical neglect as well as physical, emotional and lastly sexual abuse. This scale is a 5-point Likert-type instrument consisting of 28 items. The total score is calculated by summing the subscale scores. A cutoff value of 35 or higher is considered indicative of clinically significant symptom levels. The Turkish version

of CTQ was conducted by Şar et al. (2012) [20].

The Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS): SANS and SAPS are clinician-rated scales used to assess the severity of the negative and positive symptom dimensions of schizophrenia. Score of 0 indicates the absence of the respective symptom, whereas scores of 1 or higher indicated the presence of that symptom at any level of severity. SANS evaluates affective flattening, alogia, avolition–apathy, anhedonia–asociality, and attention, while SAPS assesses hallucinations, delusions, bizarre behavior, and thought disorder. The Turkish version of SANS and SAPS were both adapted by Erkoç et al. (1991a [21] and 1991b [22]).

2.3. Genetic polymorphism analysis

Blood samples were taken once from each patient and placed in tubes containing EDTA for genetic analysis. Genomic DNA was extracted from 200 µl blood samples in EDTA tubes. The manufacturer's instructions were followed for DNA isolation. Pure and clean DNA was successfully isolated from all blood samples collected.

A PCR-RFLP method, optimized in our previous study [11], was used to genotype the *MAOA* rs1465108 polymorphism. Briefly, PCR amplification was performed in a 25 µl reaction mixture containing 10 mM dNTP mix, 10 pmol each of forward (5'-TGGTGACTTGCCTTCAGACT-3′) and reverse (5'-ACGATTGCCCTATCACAGCA-3′) primers, 1 U Taq DNA polymerase, 10× PCR buffer, and 50 ng genomic DNA. The PCR conditions were: initial denaturation at 94 °C for 5 min, followed by 35 cycles of denaturation at 94 °C for 1 min, annealing at 60 °C for 1 min, and extension at 72 °C for 1 min. The final extension was at 72 °C for 10 min. The *HhaI* restriction enzyme was then used to digest a PCR product of 684 bp containing an A to G transition polymorphism in the intron region of *MAOA*. The digested fragments were separated by electrophoresis on a 2% agarose gel, and the genotypes were determined. While the 'A' allele gave one uncut fragment (684 bp), the 'G' allele gave 2 fragments (492 bp and 192 bp).

The PCR-RFLP method was also used for the identification of the *BDNF* rs6265 polymorphism. PCR amplification was performed in a 25 µl reaction mixture containing 0.16 µM dNTP mix, 10 pmol forward (5'-TCTGTCTTGTTTCTGCTTTCTC-3′) and reverse (5'-AATGCCTTTTGTCTATGCCC-3′) primers, 0.625 U Hot-Start Taq DNA polymerase, 1× PCR buffer, and ~ 200 ng genomic DNA. PCR conditions were as follows: initial denaturation at 95 °C for 15 min, followed by 36 cycles of denaturation at 94 °C for 1 min, annealing at 55 °C for 1.5 min, and extension at 72 °C for 1 min, followed by a final extension at 72 °C for 10 min. The 660 base pair PCR product was then digested with the *Eco72I* restriction enzyme. Digested and undigested fragments were separated by electrophoresis on a 2% agarose gel.

2.4. Statistical analyses

Data analysis was performed using SPSS version 25. The Kolmogorov-Smirnov test was employed to assess the normality of the data distribution. For normally distributed quantitative variables, the mean ± standard deviation, minimum, and maximum values were reported. For non-normally distributed data, the median and interquartile range (IQR) values were presented. For categorical variables with expected cell counts less than 5, Fisher's exact test was used, whereas the chi-square test was applied when expected cell counts were sufficient. Genotype frequencies were calculated, and adherence to Hardy–Weinberg equilibrium (HWE) was evaluated using the equation $p^2 + 2pq + q^2 = 1$. HWE was calculated for the *BDNF* rs6265 polymorphism in the entire sample, whereas for the X-linked *MAOA* polymorphism, HWE was assessed only in female participants, as males are hemizygous. Patients were stratified into three genotype groups: homozygous wild-type, heterozygous, and homozygous variant. For *BDNF* rs6265, scale scores were compared across the three genotypes according to a co-dominant model. To examine the effect of the A allele, the GA and AA genotypes were combined and compared with GG. Due to low frequency of AA genotypes ($n = 6$), genotypes could not be combined to assess the effect of the G allele. Comparisons between *BDNF* rs6265 genotype groups and scores obtained from assessment scales were conducted. For two-group comparisons, either the independent samples *t*-test or the Mann–Whitney *U* test was applied, based on the distribution of the data. For comparisons among three or more groups, one-way ANOVA or the non-parametric Kruskal–Wallis test was utilized accordingly. To evaluate the main effect of *BDNF* rs6265 genotypes on aggression, ANCOVA was conducted including age, gender, and other relevant clinical measures (Childhood Trauma Questionnaire, SAPS, SANS, and BIS-11 scores) as covariates. A General Linear Model (GLM) was employed to examine both the effect of the *MAOA* rs1465108 polymorphism and the combined effects of *BDNF* rs6265 and *MAOA* rs1465108 polymorphisms on total scores of scales because of the X-linked *MAOA* polymorphism. A *p*-value of <0.05 was considered indicative of statistical significance.

3. Results

3.1. Sociodemographic and clinical profiles by gender

The sample consisted of 150 patients diagnosed with schizophrenia, including 45 women and 105 men, with a mean age of 42.34 ± 10.41 years. Sociodemographic characteristics between male and female patients revealed statistically significant differences (Table 1). The mean age was higher in women (45.51 ± 9.56 years) compared to men (40.98 ± 10.51 years) with a meaningful statistical significance ($p = 0.014$). Male patients exhibited significantly higher rates of alcohol use ($p = 0.038$), smoking ($p = 0.005$), and disciplinary problems during school years ($p = 0.04$). Furthermore, male patients more frequently reported a history of criminal cases ($p = 0.002$) and experiences of physical or verbal violence ($p = 0.011$). In contrast, variables such as suicide attempts, self-harming behaviors, probation status, and property damage during childhood did not differ significantly between genders ($p > 0.05$).

3.2. Genetic variation and hardy–weinberg equilibrium

Genotype and allele frequencies for the *MAOA* rs1465108 and *BDNF* rs6265 polymorphisms are presented in Table 2. The genotype distributions of the *BDNF* rs6265 polymorphism conformed to Hardy–Weinberg equilibrium in the total sample ($\chi^2 = 2.42$, $p = 0.12$). For the X-linked *MAOA* rs1465108 polymorphism, Hardy–Weinberg equilibrium was assessed only in female patients and was also in equilibrium ($\chi^2 = 0.45$, $p = 0.50$). The variant allele (A) frequency of *BDNF* rs6265 was 15%. For *MAOA* rs1465108, the variant allele (G) frequency was 70% among female patients and 66.7% among male patients.

3.3. Descriptive statistics of psychometric scale scores

Detailed distributions of the BPAQ, CTQ, SAPS, SANS and BIS-11 scores in the 150 individuals included in the study are summarized in Table 3. Aggression (BPAQ) had a median score of 44.0 (IQR: 22.75–58.25), childhood trauma (CTQ) 40.0 (IQR: 33.75–51.25), positive symptoms (SAPS) 7.0 (IQR: 0.0–26.25), negative symptoms (SANS) 42.55 ± 25.39, and impulsivity (BIS-11) 28.0 (IQR: 24.0–33.0). Subscale scores for all measures are provided in Table 3.

3.4. Psychometric measures by BDNF rs6265 genotypes

To examine the association of the *BDNF* rs6265 polymorphism with aggression severity and other psychometric scale scores, comparisons were performed across genotypes using both a co-dominant model (GG, GA, AA) and an A-dominant model (GA + AA vs. GG). A G-dominant model could not be analyzed due to the small number of individuals with the AA genotype ($n = 6$). The results are presented in Table 4. In

Table 1
Sociodemographic and Clinical Characteristics of the Sample Stratified by Gender.

Sociodemographic Data		Female ($n = 45$)	Male ($n = 105$)	Total ($n = 150$)	χ^{2**} (p-value*)
Age (years) Mean ± SD (Min.-Max.)		45.51 ± 9.56 (24.0–63.0)	40.98 ± 10.51 (18.0–64.0)	42.34 ± 10.41 (18.0–64.0)	p = 0.014
Alcohol use	Yes n (%)	2 (4.4)	19 (18.1)	21 (14.0)	(p = 0.038)
	No n (%)	43 (95.6)	86 (81.9)	129 (86.0)	
Smoking	Yes n (%)	18 (40.0)	68 (64.8)	86 (57.3)	7.90 (p = 0.005)
	No n (%)	27 (60.0)	37 (35.2)	64 (42.7)	
Disciplinary action in school	Yes n (%)	1 (2.2)	14 (13.3)	15 (10.0)	(p = 0.04)
	No n (%)	44 (97.8)	91 (86.7)	135 (90.0)	
Criminal case history	Yes n (%)	2 (4.4)	27 (25.7)	29 (19.3)	(p = 0.002)
	No n (%)	43 (95.6)	78 (74.3)	121 (80.7)	
Probation	Yes n (%)	0 (0)	6 (5.7)	6 (4.0)	(p = 0.179)
	No n (%)	45 (100)	99 (94.3)	144 (96.0)	
Suicide attempt	Yes n (%)	14 (31.1)	39 (37.1)	53 (35.3)	0.50 (p = 0.479)
	No n (%)	31 (68.9)	66 (62.9)	97 (64.7)	
Criminal case in the family	Yes n (%)	4 (8.9)	9 (8.6)	13 (8.7)	(p = 1.0)
	No n (%)	41 (91.1)	96 (91.4)	137 (91.3)	
Physical/ verbal violence	Yes n (%)	8 (17.8)	41 (39.0)	49 (32.7)	6.48 (p = 0.011)
	No n (%)	37 (82.2)	64 (61.0)	101 (67.3)	
Self-harm	Yes n (%)	4 (8.9)	22 (21.0)	26 (17.3)	(p = 0.099)
	No n (%)	41 (91.1)	83 (79.0)	124 (82.7)	
Property damage in childhood	Yes n (%)	1 (2.2)	3 (2.9)	4 (2.7)	0.05 (p = 0.825)
	No n (%)	44 (97.8)	102 (97.1)	146 (97.3)	

*Compared female with male, ** Pearson's chi-square test was used when expected cell counts were sufficient (≥5); otherwise, Fisher's exact test was applied.

addition, although not part of the primary aim, we also explored the potential associations between the investigated SNPs and other clinical covariate measures. These secondary analyses were conducted to better characterize the clinical correlates of the genetic variants.

According to the A-dominant model (GA + AA vs. GG), a statistically significant difference between the genotype groups was found solely in the Planning subscale of the Barratt Impulsiveness Scale ($p = 0.021$), with the GG genotype group exhibiting higher score.

Under the co-dominant model, *BDNF* rs6265 genotype groups did not differ significantly in any Buss–Perry Aggression Questionnaire subscale (physical aggression, verbal aggression, anger, hostility) or in total aggression scores (all $p > 0.05$). Similarly, no significant differences were observed between *BDNF* rs6265 genotype groups in Barratt Impulsiveness Scale scores, Childhood Trauma Questionnaire scores, or in SAPS and SANS total and subscale scores. Although no statistically significant differences were found between *BDNF* rs6265 genotype groups, it is worth noting that patients with the GG genotype have higher scores across all scales—except for SAPS and SANS—compared to those with GA or AA genotypes.

3.5. Covariate-adjusted effects of BDNF rs6265 genotypes on aggression

ANCOVA analyses were conducted to examine the effect of *BDNF* rs6265 genotypes on aggression scores measured by the Buss-Perry Aggression Questionnaire, while controlling for childhood trauma, age, sex, as well as SAPS and SANS scores. These measures were assessed and included as covariates in the statistical analyses to control for their potential confounding.

effects on aggression. Childhood Trauma Questionnaire scores ($F = 9.11$, $p = 0.03$), total SAPS scores ($F = 5.83$, $p = 0.017$), and total SANS scores ($F = 11.73$, $p = 0.01$) significantly predicted aggression, whereas age was not a significant predictor ($F = 3.18$, $p = 0.08$). The main effects of genotype and gender were also not statistically significant ($p > 0.05$).

3.6. Association of MAOA rs1465108 with aggression

A General Linear Model (GLM) was employed to examine the effect of the *MAOA* polymorphism on total aggression scores. Given that *MAOA* is located on the X chromosome, gender was included as a fixed factor. Childhood trauma, SAPS, SANS and Barratt impulsivity scores were included as covariates in the model. The *MAOA* genotype x gender interaction was not statistically significant ($F = 0.05$, $p = 0.945$), indicating that the association between genotype and aggression did not differ by gender. After controlling for these covariates, the main effect of *MAOA* genotype was not significant ($F = 0.117$, $p = 0.89$). Among the covariates, SAPS, SANS, and Barratt impulsivity scores were significant predictors of aggression ($p > 0.05$), whereas childhood trauma showed a trend, and age was not significant. The model explained 24.2% of the variance in aggression ($R^2 = 0.242$, Adjusted $R^2 = 0.193$).

3.7. Combined effects of BDNF rs6265 and MAOA rs1465108 genotypes on scale scores

To examine the combined effects of *BDNF* rs6265 and *MAOA* rs1465108 polymorphisms on aggression and impulsivity scale scores, a General Linear Model (GLM) – Univariate analysis was conducted (Table 5). Considering that *MAOA* is located on the X chromosome, analyses were performed separately for males and females to account for genetic differences (i.e., hemizygosity in males vs. homozygosity/heterozygosity in females). In both sexes, the main effects of *BDNF rs6265* and *MAOA rs1465108* genotypes on scale scores were found to be non-significant ($p > 0.05$).

4. Discussion

Individuals with schizophrenia estimated to display aggressive behaviors three to four times more frequently than the general population. Meta-analyses have reported that nearly one-third of patients with schizophrenia exhibit aggressive behaviors during their first psychotic

Table 2
Allele and genotype frequencies of *MAOA* rs1465108 and *BDNF* rs6265 polymorphisms.

Alleles							
MAOA rs1465108	*n* = 195		% Frequency (95% Cl)		*BDNF* rs6265	*n* = 300	%Frequency (95% Cl)
A	62		31.8 (25.3–38.3)		G	254	84.67 (80.6–88.8)
G	133		68.2 (61.7–74.7)		A	46	15.33 (11.3–19.4)
Genotypes							
MAOA rs1465108	n = 45 (female)	n = 105 (male)	% Frequency (95% Cl)		*BDNF* rs6265	n = 150	% Frequency (95% Cl)
AA	5	35	11.1 (1.9–20.3)	33.3 (24.3–42.4)	GG	110	73.3 (66.3–80.4)
AG	17	–	37.8 (23.6–51.9)	–	GA	34	22.7 (16.0–29.4)
GG	23	70	51.1 (36.5–65.7)	66.7 (57.7–75.7)	AA	6	4.0 (0.9–7.1)
HWE* p-value for female patients			$\chi^2 = 0.45$ p = 0.50		HWE p-value		$\chi^2 = 2.42$ p = 0.12

n: number, CI: Confidence Interval, HWE: Hardy-Weinberg Equilibrium, * HWE was assessed only in female patients for the X-linked *MAOA* rs1465108 polymorphism.

Table 3
Detailed distributions of the BPAQ, CTQ, SAPS, SANS and BIS-11 scores in Patients with Schizophrenia (n = 150).

Scale / Subscale	Score Type	Value
Buss-Perry Aggression Questionnaire (BPAQ)		
Total aggression	Median (IQR)	44.0 (22.75–58.25)
Physical aggression	Median (IQR)	11.0 (4.0–16.5)
Verbal aggression	Median (IQR)	8.0 (4.0–10.0)
Anger	Median (IQR)	9.5 (5.0–15.0)
Hostility	Mean ± S.D. (Range)	13.47 ± 7.55 (0.0–34.0)
Childhood Trauma Questionnaire (CTQ)		
Total CTQ score	Median (IQR)	40.0 (33.75–51.25)
Scale for the Assessment of Positive Symptoms (SAPS)		
Total SAPS score	Median (IQR)	7.0 (0.0–26.25)
Hallucinations	Median (IQR)	0.0 (0.0–7.25)
Delusions	Median (IQR)	1.5 (0.0–9.0)
Bizarre behavior	Median (IQR)	0.0 (0.0–3.0)
Scale for the Assessment of Negative Symptoms (SANS)		
Total SANS score	Mean ± SD (Range)	42.55 ± 25.39 (0–114)
Affective flattening	Median (IQR)	12.0 (6.75–20.0)
Alogia	Median (IQR)	4.0 (0.0–10.0)
Avolition–apathy	Median (IQR)	8.0 (3.0–13.0)
Anhedonia–asociality	Median (IQR)	15.0 (6.75–19.0)
Attention	Median (IQR)	2.0 (0.0–6.0)
Barratt Impulsiveness Scale (BIS-11)		
Total impulsivity	Median (IQR)	28.0 (24.0–33.0)
Non-planning impulsivity	Median (IQR)	11.0 (8.75–13.25)
Motor impulsivity	Median (IQR)	8.0 (6.0–10.0)
Attentional impulsivity	Median (IQR)	9.0 (8.75–13.25)

episode. Aggressive behaviors in schizophrenia are typically linked to positive symptoms and tend to decrease with the use of antipsychotic medications. However, the persistently high prevalence of aggression among patients with schizophrenia, even when other contributing factors are controlled, suggests that additional factors, such as genetic variations, may also play a role. Notably, to date, no studies have specifically investigated the influence of genetic variations on aggressive behaviors in patients with schizophrenia.

The first evidence shedding light on the neurogenetic basis of aggressive behavior was reported in 1993 from a study conducted on a large Dutch family [23]. Several males in this family exhibited borderline intellectual disability along with abnormal violent behaviors such as impulsive aggression, arson, attempted rape, and exhibitionism. In these individuals, a point mutation was identified in exon 8 of the monoamine oxidase A (*MAOA*) gene. This finding demonstrated that MAOA, an enzyme critical in the catabolism of biogenic amines, may play a crucial role in regulating impulsive aggression. Moreover, due to the established association between low serotonin levels and heightened aggressive behavior, these results directed attention to serotonin as a key neurotransmitter. Consequently, genes involved in the regulation of serotonergic and catecholaminergic systems are considered to be major contributors [24]. Studies on MAO-A knock-out mice have demonstrated that the absence of this enzyme leads to marked aggression, maladaptive defensive behaviors, and repetitive responses [25]. Zaal and Saud (2024) observed an association between reduced MAOA levels and increased violence in prisoners compared with controls [26]. Although evidence on the association between BDNF and schizophrenia remains inconclusive, the diverse functions of BDNF in brain tissue suggest a potential role in the pathophysiology of schizophrenia. Postmortem studies in patients with schizophrenia have revealed alterations in BDNF levels across specific brain regions. Recent investigations have shown increased *BDNF* expression in the frontal cortex and hippocampus of patients compared to controls [27], while other studies have reported reduced levels of BDNF and its receptor TrkB in cortical regions [28]. Studies aiming to identify the genes involved in aggressive behavior suggest that aggression is a complex biological trait governed by the interaction of multiple genes and proteins. Building on this background, the present study specifically focused on the *BDNF* and *MAOA* genes.

The *BDNF* gene is highly polymorphic, with more than 40 single nucleotide polymorphisms (SNPs) reported in previous studies [29]. Among these, two *BDNF* polymorphisms have been widely investigated for their association with schizophrenia worldwide: rs6265 and rs27656701. Of these variants, rs6265 (Val66Met; G196A) has been the most extensively studied. At the molecular level, the *BDNF* rs6265 polymorphism involves a nucleotide substitution from guanine to adenine at position 196 (G196A) within codon 66 of the proBDNF sequence, resulting in an amino acid change from valine to methionine. This substitution has been shown to markedly affect protein activity, influencing processes such as signal transduction, antigen–antibody recognition, intracellular trafficking, and hormone function, and has also been implicated in several neurodegenerative disorders including Alzheimer's, Huntington's, Parkinson's disease, and dementia. The *BDNF* rs6265 polymorphism, observed in more than 25% of the human population, has been reported to alter the intracellular trafficking and secretion of mature BDNF, thereby affecting hippocampal function [30]. These findings are further supported by animal studies showing that alterations in mature BDNF levels in rodents lead to hippocampal dysfunction and behavioral abnormalities [31]. Furthermore, because rs6265 is located within a DNase I hypersensitive region, it has been suggested that the polymorphism may influence transcription factor binding and thereby modulate mRNA expression. Conversely, other studies have indicated that rs6265 does not affect BDNF mRNA

Table 4
Psychometric scale scores across *BDNF* rs6265 genotypes using co-dominant (GG, GA, AA) and A-allele dominant (GA + AA vs. GG) models.

Scales	Genetic Model	N	Median (IQR) or Mean ± S.D	p-value
	Co-dominant			
Buss-Perry Physical Aggression**	GG	110	12.0 (6.75–17.0)	H = 5.77
	GA	34	10.5 (2.0–16.0)	*p* =
	AA	6	2.5 (0.0–10.0)	0.056
Median (IQR)	A-dominant			
	GA + AA	40	9.0 (1.25–15.75)	U =
	GG	110	12.0 (6.75–17.0)	1888.0
				Z =
				-1.328
				p =
				0.184
	Co-dominant			
Buss-Perry Verbal Aggression**	GG	110	8.0 (5.0–10.0)	H =
	GA	34	7.0 (4.0–10.0)	0.929
	AA	6	5.5 (4.5–11.0)	*p* =
Median (IQR)				0.628
	A-dominant			
	GA + AA	40	6.0 (4.0–10.0)	U =
	GG	110	8.0 (5.0–10.0)	1974.5
				Z =
				-0.961
				p =
				0.336
	Co-dominant			
	GG	110	10.0 (6.0–15.0)	H =
Buss-Perry Anger**	GA	34	8.5 (3.0–16.25)	1.147
	AA	6	9.0 (4.0–12.0)	*p* =
Median (IQR)				0.564
	A-dominant			
	GA + AA	40	8.5 (3.0–14.75)	U =
	GG	110	10.0 (6.0–15.0)	1968.0
				Z =
				-0.987
				p =
				0.324
	Co-dominant			
Buss-Perry Hostility*	GG	110	13.84 ± 7.56 (0.0–34.0)	F = 1.032
mean ± S.D. (min.-max.)	GA	34	12.97 ± 7.7 (0.0–27.0)	*p* = 0.359
	AA	6	9.5 ± 5.58 (4.0–20.0)	
	A-dominant			
	GA + AA	40	12.45 ± 7.47 (0.0–28.0)	*t* = 0.993
	GG	110	13.84 ± 7.58 (0.0–34.0)	*p* = 0.322
	Co-dominant			
Buss-Perry Total score**	GG	110	46.0 (25.0–60.0)	H =
	GA	34	37.0 (17.75–58.25)	3.249
Median (IQR)	AA	6	30.5 (19.25–36.25)	*p* = 0.197
	A-dominant			
	GA + AA	40	32.5 (18.25–56.5)	U =
	GG	110	46.0 (25.5–60.0)	1902.0
				Z =
				-1.267
				p =
				0.205
Barratt Impulsiveness Scale (BIS-11)/Total**	Co-dominant			
	GG	110	28.0 (25.0–34.0)	H =
	GA	34	27.0 (23.0–33.25)	4131
Median (IQR)	AA	6	23.5 (22.0–27.0)	*p* =
				0.127
	A-dominant			
	GA + AA	40	27.0 (23.0–32.75)	U =
	GG	110	28.0 (25.0–34.0)	1895.0
				Z =
				-1.298
				p =
				0.194

Table 4 (*continued*)

Scales	Genetic Model	N	Median (IQR) or Mean ± S.D	p-value
	Co-dominant			
BIS-11/ non-planning impulsivity**	GG	110	11.00 (9.00–14.00)	H = 5.564
	GA	34	10.00 (7.75–12.00)	*p* = 0.062
Median (IQR)	AA	6	10.00 (5.75–12.00)	
	A-dominant			
	GA + AA	40	10.0 (7.25–12.0)	U =
	GG	110	11.0 (9.00–14.00)	1657.5,
				Z =
				-2.315
				p =
				0.021
	Co-dominant			
BIS-11/ Motor impulsivity**	GG	110	8.00 (6.00–10.00)	H =
	GA	34	8.00 (6.00–11.00)	1.301
	AA	6	6.50 (4.25–9.75)	*p* =
Median (IQR)				0.522
	A-dominant			
	GA + AA	40	8.0 (5.25–11.0)	U =
	GG	110	8.0 (6.0–10.0)	2180.5,
				Z =
				-0.392
				p =
				0.695
	Co-dominant			
BIS-11/ Attentional impulsivity**	GG	110	9.50 (7.75–11.00)	H =
	GA	34	10.00 (7.00–12.00)	0.562
				p =
Median (IQR)	AA	6	9.00 (6.50–9.75)	0.775
	A-dominant			
	GA + AA	40	9.0 (7.0–11.75)	U =
	GG	110	9.5 (7.75–11.0)	2170.0,
				Z =
				-0.128
				p =
				0.898
	Co-dominant			
Childhood Trauma Questionnaire**	GG	110	40.5 (34.0–51.25)	H =
	GA	34	38.0 (33.0–58.25)	0.152
	AA	6	36.0 (31.5–58.75)	*p* =
Median (IQR)				0.927
	A-dominant			
	GA + AA	40	37.0 (33.0–56.25)	U =
	GG	110	40.5 (34.0–51.25)	2146.5
				Z =
				-0.227
				p =
				0.820
	Co-dominant			
Positive Syndrome Scale (SAPS)**	GG	110	6.0 (0.0–27.5)	H =
	GA	34	8.0 (0.75–21.5)	0.466
	AA	6	6.5(0.0–17.5)	*p* =
Median (IQR)				0.792
	A-dominant			
	GA + AA	40	8.0 (0.25–20.5)	U =
	GG	110	6.0 (0.0–27.5)	2227.5
				Z =
				-0.314
				p =
				0.727
	Co-dominant			
Negative Syndrome Scale (SANS)*	GG	110	42.25 ± 25.9 (0.0–14.0)	F = 0.190
	GA	34	42.44 ± 24.0 (0.0–92.0)	*p* = 0.827
Mean ± S.D. (min.-max.)	AA	6	48.83 ± 25.9 (4.0–78.0)	
	A-dominant			
	GA + AA	40	43.4 ± 24.1 (0.0–92.0)	*t* = −0.245
	GG	110	42.2 ± 26.0 (0.0–114.0)	*p* = 0.806

*Normal variables: mean ± S.D.; one-way ANOVA: F and p; independent samples t-test: t and p (from SPSS). **Non-normal variables: median (IQR); Kruskal–Wallis: H and p; Mann–Whitney: U, Z and p (from SPSS).

expression directly but rather alters the availability of BDNF protein [17].

In this study, the potential association of the *BDNF* rs6265 polymorphism with aggression was examined. The findings revealed no statistically significant differences among genotype groups in any of the BPAQ subscale scores as well as BPAQ total scores. Likewise, no significant differences were observed between genotype groups in the BIS-11, CTQ, SAPS, or SANS scores. Nevertheless, it is noteworthy that participants with the GG genotype consistently tended to score higher across all measures. While this trend did not reach statistical significance, it may reflect a clinically relevant pattern that warrants further investigation in studies with larger sample sizes.

Neither the *BDNF* rs6265 genotype nor gender showed a statistically significant main effect on aggression scores. However, under the A-dominant genetic model, a significant difference emerged in the Planning Subscale of the BIS-11, with the GG group exhibiting higher scores ($p = 0.021$). This finding is consistent with previous reports indicating that the GG (Val/Val) genotype is associated with elevated scores on certain clinical parameters, such as PANSS general psychopathology subscale [32]. Impaired planning abilities may reflect challenges in organizing behavior and engaging in goal-directed thinking. These results are also in line with neuroimaging evidence suggesting that the GG genotype may be linked to deficits in cognitive processes related to prefrontal cortex functioning [33].

Several studies in the literature have identified significant associations between the *BDNF* rs6265 polymorphism and aggression or impulsivity. For instance, Spalletta et al. (2010) reported that carriers of the A allele had higher aggression scores [34], while Bi et al. (2018) demonstrated an interaction between childhood trauma and the *BDNF* rs6265 polymorphism, particularly in behavioral domains such as sensation seeking, anger, and impulsivity [35]. Conversely, other studies have failed to replicate a significant association between this polymorphism and aggression [36]. Kumar et al. (2020) demonstrated that the functional polymorphism rs6265 shows no association with serum BDNF levels [37]. Taken together, these conflicting findings suggest that genetic influences alone are unlikely to fully account for behavioral phenotypes. Instead, a complex interplay between genetic predisposition, developmental history, environmental stressors, and co-occurring psychopathology must be considered. Therefore, careful attention to gene–environment interactions is essential when interpreting such results.

ANCOVA analysis was also performed to control for the effects of childhood trauma, positive symptoms, and negative symptoms on aggression scores. The results indicated that CTQ ($F = 9.11$, $p = 0.03$), SAPS ($F = 5.83$, $p = 0.017$), and SANS ($F = 11.73$, $p = 0.01$) scores significantly influenced total aggression scores as measured by BPAQ. These findings align with previous literature underscoring the critical role of early-life stressors in the development of neuropsychiatric disorders and impaired behavioral regulation [38]. Consistently, a recent study reported that childhood trauma was associated with functional impairments in the prefrontal cortex, which in turn contributed to reduced impulse control and heightened aggressive tendencies [39].

This study also evaluated the association of the *MAOA* rs1465108 polymorphism with aggression in patients with schizophrenia. General Linear Model (GLM) analyses showed that genotype x gender interaction

Table 5
Combined main effects of *BDNF* rs6265 and *MAOA* rs1465108 genotypes on BPAQ and BIS-11 scores in male and female participants (GLM–Univariate analysis).

Gender	*BDNF* rs6265	Scales					
		Buss-Perry Aggression Questionnaire (BPAQ)			Barratt Impulsiveness Scale-11 (BIS-11)		
		MAOA rs1465108			*MAOA* rs1465108		
		AA	AG (n = 1)	GG (n = 1)	AA	AG (n = 1)	GG (n = 1)
Women	AA		33.0 (33.00–33.00)	43.0 (43.00–43.00)		24.0 (24.0–24.0)	22.0 (22.0–22.0)
		AA	AG	GG	AA	AG	GG
			(n = 4)	(n = 2)		(n = 4)	(n = 2)
	AG		46.5 (22.5–62.25)	41.0 (30.0-)		27.0 (17.75–37.75)	21.00 (15.0-)
		AA	AG	GG	AA	AG	GG
		(*n* = 5)	(*n* = 12)	(*n* = 20)	(n = 5)	(n = 12)	(n = 20)
	GG	47.0 (31.0–75.0)	46.0 (37.5–61.13)	45.0 (26.25–60.88)	28.0 (24.5–34.5)	26.0 (20.5–33.25)	28.5 (24.0–37.5)
p*	F = 0.179		F = 0.241			–	
	p = 0.837		*p* = 0.787				
p**	F = 0.571		–			F = 0.030	
	p = 0.570					*p* = 0.970	
Men	*BDNF* rs6265		*MAOA* rs1465108			*MAOA* rs1465108	
		AA	AG	GG	AA	AG	GG
		(n = 2)		(n = 2)	(n = 2)		(*n* = 2)
	AA	27.5 (21.0-)		21.0 (14.0-)	22.5 (22.0-)		28.0 (28.0-)
		AA	AG	GG	AA	AG	GG
	AG	(*n* = 11)		(*n* = 17)	(n = 11)		(n = 17)
		58.0 (16.0–72.0)		24.0 (18.0–55.0)	33.0 (27.0–40.0)		27.0 (23.5–30.5)
		AA	AG	GG	AA	AG	GG
	GG	(*n* = 22)		(*n* = 51)	(*n* = 22)		(n = 51)
		40.0 (21.0–55.25)		47.0 (23.0–61.0)	30.0 (23.5–33.75)		29.0 (26.0–34.0)
p*	F = 1.267		F = 0.185			–	
	p = 0.286		*p* = 0.668				
p**	F = 1.068		–			F = 0.067	
	p = 0.347					*p* = 0.796	

*: Buss-Perry Aggression Questionnaire, ** Barratt Impulsiveness Scale.

had no statistically significant effect on aggression levels ($F = 0.05$, $p = 0.945$). In contrast, SAPS, SANS, and Barratt impulsivity scores were significant predictors of aggression and childhood trauma showed a trend effect on aggression. Previous studies have highlighted the role of early-life stress in shaping psychopathological outcomes. For example, research in a Chinese population suggested that early onset of schizophrenia, anxiety symptoms, suicidal tendencies, and aggressive behaviors may be associated with childhood trauma [40]. Furthermore, gene–environment interaction studies have shown that individuals with the low-activity MAOA variant—particularly males—or the high-activity variant in females display higher levels of aggressive behavior in adulthood when exposed to childhood trauma [41]. Aggression, which is strongly associated with both criminal and suicidal behavior, is also considered among the positive symptoms of schizophrenia. Supporting this, Iancu et al. (2010) reported that aggression, high impulsivity, and positive symptoms were related to suicidal ideation and attempts in patients with schizophrenia [42]. Taken together, these findings suggest that aggression in schizophrenia are shaped by environmental factors and clinical characteristics. Importantly, the *MAOA* rs1465108 variant was not found to be a determining factor in this study.

In a study of alcohol-dependent individuals, the *MAOA* GG genotype was observed in 79.2% of those with a history of aggression, compared to 51.9% among individuals with only a suicide attempt, where the AG genotype was also more frequent (18.5%). These findings suggest that the GG genotype may be more closely associated with aggression, whereas the presence of the A allele (AG or AA) may be linked to autoaggressive behavior. However, statistical significance was not reported, and the relatively small sample size limits the interpretation of these results [43]. In line with this, Chester et al. (2015) demonstrated that the rs1465108 polymorphism exerts an indirect effect on aggression. Specifically, the low-functioning A allele was shown to increase aggression through negative urgency—defined as impulsive reactions to negative emotions—a pathway that was statistically significant [12]. These findings suggest that the association of the *MAOA* rs1465108 polymorphism with aggression may not be uniform, but rather dependent on diagnosis, environmental exposures, and individual psychological characteristics.

The patients were also evaluated in terms of alcohol and cigarette use, disciplinary actions at school, history of criminal incidents, suicide attempts or self-harming behaviors, and physical/verbal violence. In this sample, 14% of the patients reported alcohol use, while 57.33% were smokers. Additionally, 10% had received disciplinary punishment at school, and 2.67% reported a history of property damage in childhood. Previous research has consistently shown that individuals with schizophrenia are at greater risk of violent behavior compared to control groups (4). In our study, 19.33% of the patients had a criminal record, 4% had probation, and 32.67% reported a history of physical or verbal violence. For comparison, a study conducted in Turkey with 208 patients reported a lower rate of criminal history (2.4%) [44]. The prevalence of suicide attempts in individuals with schizophrenia has been reported to range between 18% and 55% [45]. In the present study, 17.33% of the patients had engaged in self-harming behaviors, and 35.33% had attempted suicide. The rates of criminal records and suicide attempts in this sample appear to be broadly consistent with findings from the literature.

In conclusion, this cross-sectional study allows the examination of associations—specifically between genotype and symptom ratings obtained from clinical scales—thereby providing insights into potential relationships among variables. However, due to its cross-sectional design, causality cannot be inferred. Our findings underscore the multifactorial nature of aggression in schizophrenia, as neither the *BDNF* rs6265 nor the *MAOA* rs1465108 polymorphisms demonstrated a direct or statistically significant association with aggression-related behavioral traits. Although the *BDNF* GG genotype exhibited a non-significant trend toward higher aggression, and planning skills were significantly associated under the A-dominance model, the *MAOA* variant did not predict aggression in this sample. Instead, environmental and clinical variables—including childhood trauma, impulsivity and positive and negative symptoms—emerged as significant modulators of aggressive behaviors, emphasizing the importance of early life stressors and psychopathological features. The observed associations between impulsivity and elevated aggression further underscore the importance of gene–environment interactions in shaping behavioral outcomes in schizophrenia. Additionally, sociodemographic factors such as age and gender followed expected patterns in line with previous research, whereas genotype effects remained inconclusive. Taken together, these findings suggest that behavioral dysregulation in schizophrenia arises from a complex interplay between genetic susceptibility, developmental adversities, and clinical symptomatology, pointing to the need for holistic approaches in both future research and clinical management.

CRediT authorship contribution statement

Sariye Aybüke Yıldırım: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Irmak Dal:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Selin Özkan-Kotiloğlu:** Supervision, Resources, Methodology, Investigation, Conceptualization. **Fatih Özdemir:** Methodology, Investigation, Data curation, Conceptualization. **Osman Topçu:** Methodology, Investigation, Data curation, Conceptualization. **Burçin Çolak:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Bora Baskak:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Dilek Kaya-Akyüzlü:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We acknowledge the use of ChatGPT (OpenAI) as an AI-based language support tool in improving the clarity and readability of the English text.

Data availability

Data will be made available on request.

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