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Association of catechol-o-methyltransferase (COMT) gene rs4680 polymorphism and risk of obsessive-compulsive disorder in a clinically characterized Bangladeshi cohort

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Abstract

Background The catechol-O-methyltransferase (*COMT*) gene is crucial for breaking down dopamine. The Val158Met polymorphism (rs4680) affects its enzymatic activity. Our study aims to assess the association of the rs4680 (Val158Met) polymorphism in the *COMT* gene with obsessive-compulsive disorder (OCD) among Bangladeshi population.

Methods We conducted a case-control study with 90 OCD patients and 90 healthy controls, matched by age and gender. The participants had been recruited from the Psychiatry Department of Bangladesh Medical University (BMU), Dhaka. Genomic DNA was isolated from each participant's blood sample, and the genotyping of the rs4680 polymorphism was investigated utilizing PCR-RFLP analysis.

Results The GA genotype was detected at a significantly greater frequency in OCD patients (38.89%) than in the control group (21.11%) (OR = 2.59, $p = 0.005$). The A allele also showed a significant association with OCD risk (OR = 2.41, $p = 0.002$). Female patients demonstrated stronger associations in the GA genotype comparison (OR = 2.89, $p = 0.025$), dominant model (OR = 3.22, $p = 0.010$), and A allele comparison (OR = 2.84, $p = 0.007$), whereas male patients showed no statistically significant associations.

Conclusion The findings of our study suggest that the *COMT* Val158Met polymorphism may have association with OCD risk in this cohort, with an increased susceptibility found among females. The A allele was also significantly linked to increased OCD risk in females, but not in males. More extensive studies are necessary to explore these observations with larger and more diverse populations.

Clinical trial number Not applicable.

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Keywords Catechol-o-methyltransferase gene, rs4680, Genotype, Polymorphism, Obsessive compulsive disorder, Mental health

1 Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder marked by persistent and intrusive thoughts, images, or impulses, referred to as obsessions. These often result in recurrent behaviors or mental processes, referred to as compulsions, which are carried out in response to anxiety triggered by the obsessions [1, 2]. Obsessions are typically thoughts, images or urges that invade normal thinking and relate to feelings of anxiety, discomfort, unease or a sense that something is wrong. When individuals feel compelled to carry out mental acts or behaviors over and over in response to an obsession, it is called compulsion [3]. These behaviors are usually carried out either in direct response to an obsession - hence the name, or in accordance with strict internalized rules. For instance, a person with an obsession related to contamination may experience severe anxiety, which leads to repeated washing to relieve the distress [4]. In OCD, the obsessions continue to reappear, maintaining a persistent cycle of anxiety and compulsive behavior [5].

OCD is estimated to affect between 1 and 3% of individuals over the course of a lifetime with prevalence varying across different countries [6–8]. Most individuals diagnosed with OCD tend to exhibit at least one co-occurring psychiatric disorder. Most linked conditions include major depressive disorder (MDD), generalized anxiety disorder (GAD), specific phobias, and social anxiety disorder. Among these, major depression is notably the most common long-term comorbid condition seen in individuals with OCD across various populations [9]. Epidemiological data reveal gender-based differences in diagnosis, with adult women being diagnosed with OCD more frequently than men, at rates of approximately 1.8% and 0.5% respectively [10, 11]. In contrast, during childhood, OCD appears to be more commonly identified in boys than in girls, suggesting a multifaceted interaction of biological, hormonal, and sociocultural factors. Symptoms of obsessive-compulsive behavior typically emerge during early developmental stages, with roughly 25–33% of cases presenting before the age of fourteen [12].

Public health in Bangladesh is significantly impacted by the burden of OCD, reflecting global prevalence trends while also being shaped by the nation's unique cultural, social, and economic dynamics. Recent investigations indicate that approximately 2% to 3% of the Bangladeshi population is affected by OCD, a prevalence rate consistent with international estimates [13]. Especially, adolescents and young adults appear to be disproportionately affected, with studies reporting that around 2.5% of individuals in this age group exhibit clinical symptoms associated with OCD [14]. The recognition and effective treatment of OCD in Bangladesh remain limited, primarily due to widespread stigma, low public awareness, and inadequate access to mental health services [15]. These challenges become even more difficult due to cultural beliefs about OCD symptoms which leads to delays in seeking proper medical help [16]. Epidemiological studies within the country indicate a slightly higher prevalence among women, with estimates around 3%, compared to approximately 2% in men. This gender disparity may be influenced by psychosocial stressors and societal expectations uniquely experienced by women [17].

Multiple studies have recognized dopamine dysregulation as a significant contributor to the onset of OCD [18–20]. The level of dopamine in neurons is affected by the activity of the catechol-o-methyl transferase (COMT) enzyme. It works by shifting a methyl (-CH_3) group from S-adenosylmethionine to catecholamines which include norepinephrine, epinephrine and dopamine leading to their deactivation [21]. These chemicals are essential for mood regulation, cognitive control, and the body's response to stress. Maintaining a proper balance of neurotransmitters is crucial to avoid overstimulation of receptors, which can contribute to neurological and psychiatric disorders. One of the primary roles of COMT in the brain is to metabolize dopamine in the prefrontal cortex (PFC) [22]. Regulating dopamine concentrations in this region is essential, as both excess and deficiency can impair cognitive function and may contribute to the onset of OCD [23].

The position of *COMT* gene is on the long arm (q arm) of chromosome 22 at position q11 and is abundantly expressed in the brain [24]. It shows high activity in regions such as the hippocampus and PFC [25]. The *COMT* gene is known to be genetically polymorphic and can undergo variations that influence its functions. These variations may affect how efficiently the enzyme breaks down neurotransmitters [26]. Among the most extensively investigated variants is the Val158Met polymorphism (G to A), referenced as rs4680 (NM_000754.4: c.472G > A; p.Val158Met) [27]. Although rs4680 is a common variant and is not considered pathogenic in the Mendelian sense, it remains biologically relevant because it is a functional polymorphism that affects COMT enzymatic activity [28]. This single nucleotide change causes valine (Val) at 158 of the COMT enzyme to be substituted by methionine (Met), significantly decreasing its enzymatic activity [29]. The Val-to-Met change in the COMT enzyme, which is crucial for dopamine breakdown in the PFC, results in elevated dopamine

concentrations in this specific brain area [30]. This functional polymorphism has been shown to produce a three to four-fold variation in enzymatic efficiency [31, 32]. Studies using both recombinant proteins and post-mortem brain tissue have revealed that the Met158 variant is significantly less thermostable, which contributes to its reduced enzymatic activity. Specifically, research on post-mortem prefrontal cortex samples found that individuals with homozygous Met/Met genotype exhibited COMT activity at approximately 25%, Val/Met heterozygotes at 48%, and Val/Val homozygotes at 100% demonstrating a clear genotype-dependent deviation of enzymatic function [33]. As COMT is known to play an essential role in the metabolization of dopamine and has been implicated as a potential candidate gene for OCD, this study aims at exploring association of common missense SNP - rs4680(Val158Met) within the *COMT* gene with susceptibility to OCD among Bangladeshi population using case-control design considering both the overall sample and gender-specific subsamples.

2 Materials and methods

2.1 Subjects and psychiatric assessment

The current case-control study comprised 90 cases of OCD and equal numbers of healthy controls (HCs). The study participants were enrolled from the Psychiatry Department at Bangladesh Medical University (BMU), Dhaka, Bangladesh in between 01/04/2024 and 30/09/2024. An official approval was granted prior to study commencement from the Institutional Review Board. A psychiatric evaluation was performed for each participant. OCD diagnosis was established according to DSM-5 criteria as assessed by independent interviews conducted by two clinical interviewers [34]. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) is a clinician-rated scale that provides scores between 0 and 40, with separate sub-scores for compulsions and obsessions [35]; each of these ten items can range from zero to four: the higher the overall score means more severe symptoms. Exclusion criteria: comorbid psychiatric illness (such as major depressive disorder, bipolar disorder, schizophrenia, psychotic disorders, or substance-use disorders), major systemic medical illnesses (e.g., diabetes or liver disease), epilepsy and uncontrolled hypertension, pregnancy and current or recent use of psychotropic medications. Excluding these comorbidities reduced the sample size but yielded a more clinically homogeneous OCD cohort. Control participants were healthy individuals visiting BMU for routine health check-ups. They were screened through structured interviews and were deemed healthy by the physician at the time of recruitment. Exclusion criteria for controls were: (1) a neurological or psychiatric illness, and (2) personal or family history of psychiatric illness or use of psychotropic medications. Controls were age- and gender-matched to the patients. Ethnicity, age and family history with regional information were obtained by in-person interviews for all participants. We briefed about the purpose of this study to the subjects before participation and obtained written informed consent from the participants before data collection, in accordance with the principles of the Declaration of Helsinki. For individuals with no formal education, the consent form was read aloud, the procedures were explained verbally, and thumbprint consent was obtained in the presence of a witness. The participants' confidentiality, names or personal identifiers were kept confidential.

2.2 Sample size calculation

We determined the optimal sample size needed for this study. The estimated sample supports adequate statistical power to detect meaningful effects for comparing means, proportions, multiple groups, categorical associations, and building predictive models between the groups. We have considered the statistical power, significance level, effect size, and allocation ratio as 90%, 5%, 50%, and 1:1, respectively. Based on the above assumptions, the minimum sample size required for this study was 172 (86 cases and 86 controls). Therefore, we have recruited 90 cases and 90 controls for this study. Also, we performed population stratification for this case-control study by enrolling case and control groups from similar ancestral backgrounds.

2.3 Blood samples and DNA isolation

For the patient and control groups, venous blood samples were drawn into EDTA tubes and frozen into − 20 °C until analyzed. The genomic DNA was then extracted following the FavorPrep Blood Genomic DNA Extraction Mini Kit instructions.

2.4 Genotyping

After DNA extraction from the blood samples, we conducted PCR amplification and then the RFLP assay to genotype the (G to A) transition in the *COMT* gene. The rs4680 polymorphism of *COMT* gene was detected by amplifying a 186-bp fragment using primers 5′-GGAG CTGGGGGCCTAC TGTG-3′ (forward) and 5′- GGCC CTTTTTCCAGGTCT GACA – 3′(reverse). Total volume of reaction mix for PCR was 25 µL, including: 20 ng template DNA; primers at 10 pmol concentration each; Kapa Taq buffer (1× final conc); dNTPs (0.2 mM), $MgCl_2$ (1.5mM), and Kapa Taq polymerase (Invitrogen). The thermal cycling conditions were the initial denaturation for 10 min at 94 °C and 35 amplification cycles consisting of one minute at 94 °C for denaturation, 30 s at 59 °C for annealing and one minute at 72° C for extension with the last extension for 10 min at 72 °C. The PCR products

were treated with 5U NlaIII (sourced from New England Biolabs, USA) at 37 °C for two hours, in a volume of 12µL. The digested fragments were electrophoretically separated by means of a 5% SeaKem® LE agarose gel prepared in TBE buffer, and the gel was subsequently stained with an appropriate dye. Samples can be run at 85 V for 40 min and the intercalating agent that can be used includes 5 mg/mL ethidium bromide. A 50 bp Molecular biology grade DNA ladder (Takara Bio Inc Japan) was employed. Last of all, the gel was viewed under UV light using the gel documentation system for purposes of displaying the sample gel (Table 1).

2.5 Statistical analysis

We used the Statistical Package for the Social Sciences (SPSS) software, version 30.0 for data analysis. Hardy–Weinberg equilibrium (HWE) was assessed using the chi-square goodness-of-fit test, and a p-value > 0.05 was considered consistent with equilibrium. We calculated genotype, allele frequencies and odds ratios. The association between the rs4680 polymorphism and OCD was evaluated by Fisher's exact test and chi-square test. Moreover, 95% confidence intervals (CIs) were computed and *p*-values below 0.05 were regarded as statistically significant.

3 Results

3.1 Characteristics of study population

The characteristic description of the study population is presented in Table 2. Both the OCD patient group ($n = 90$) and HCs ($n = 90$) had an identical mean age of 29.52 ± 0.92 years and 29.7 ± 0.90 years, respectively, with no significant difference ($p = 0.890$). Age group distribution (18–25, 26–35, 36–45, 46–60) was similar between groups. Gender distribution was balanced (OCD: 46.67% male, 53.33% female; Controls: 47.78% male, 52.22% female; $p > 0.999$). Other parameters such as marital status, occupation, education level, economic conditions and residence area between two groups were similar. The average Body Mass Index (BMI) was identical in both OCD patients (23.3 ± 0.44 kg/m²) and HCs (23.63 ± 0.42 kg/m²), showing no statistically significant difference ($p > 0.05$). In terms of smoking history, 91.11% of OCD patients and 92.22% of controls were non-smokers, with no significant difference ($p > 0.999$). While comparing the previous history of OCD a significant difference was found, with 14.44% of OCD patients reporting prior episodes, while none of the controls had such history ($p < 0.001$). For family history of OCD, 13.33% of OCD patients and 4.44% of controls reported a positive family history; this difference materialized but was not statistically significant ($p > 0.05$). The mean DSM-5 score was significantly different ($p < 0.001$) between the patient (7.07 ± 0.92) and the healthy controls (0.19 ± 0.062). Likewise, the Y-BOCS scores were markedly higher in the patient group compared to controls (22.63 ± 0.703 vs. 0.04 ± 0.021, $p < 0.001$). These findings suggest strong statistical relevance in both diagnostic measures.

3.2 Clinical and laboratory findings

In the analysis of *COMT* rs4680 (Val158Met) polymorphism, digestion of the 186 bp PCR product produced distinct restriction fragment patterns for each genotype. The homozygous GG genotype showed bands at 114 bp, 40 bp, and 32 bp, whereas the homozygous AA genotype showed bands at 96 bp, 40 bp, 32 bp, and 18 bp. The heterozygous GA genotype showed all expected fragments at 114 bp, 96 bp, 40 bp, 32 bp, and 18 bp. Because the 18 bp, 32 bp, and 40 bp fragments were too small to be clearly resolved on the gel, genotype interpretation was based primarily on the presence or absence of the 114 bp and 96 bp bands (Fig. 1). The observed band patterns for the *COMT* rs4680 polymorphism were consistent with previously documented research articles, affirming the reliability of the genotype identification and distribution within the studied population.

3.3 Correlation of different genotypes with OCD

The distribution of genotypes in patients and healthy control groups obeyed Hardy-Weinberg equilibrium (Table 3, cases: $\chi^2 = 0.034$, $p = 0.85$; HCs: $\chi^2 = 0.76$, $p = 0.38$). In Table 4, the distribution of rs4680

Table 1 Primer sequences, PCR condition and fragments' size

Gene and Enzyme	Primer Sequence	PCR Condition	Fragments, BP
	F-Forward, R-Reverse		
COMT rs4680 And NlaIII	F5′-GGAGCTGGGGGCCTACTGTG-3′ R5′-GGCCCTTTTTCCAGGTCT GACA – 3′	10 min of initial denaturation at 94 °C; 35 cycles of 94 °C for 1 min, 59 °C for 30s, 72 °C for 1 min; The final extension was at 72 °C for 10 min	PCR product: 186 bp GG Common homozygote (32 bp, 40 bp, 114 bp) GA Heterozygote (18 bp, 32 bp, 40 bp, 96 bp, 114 bp) AA Rare homozygote (18 bp, 32 bp, 40 bp, 96 bp)

Note: PCR reactions (25 µL total volume) contained: 20 ng template DNA (2 µL), 10 pmol each of forward and reverse primers (2 µL each), PCR 2X master mix (10 µL), and nuclease-free water (9 µL). Restriction digestion reaction contained: PCR amplified product (8 µL), 10X QuickCut buffer (1 µL), 5U NlaIII enzyme (1µL) and nuclease-free water (2 µL)

Table 2 Socio-demographic data of OCD patients and healthy controls

Parameters	OCD patients ($n=90$)			Healthy controls ($n=90$)			*p*-value
	n	%	Mean ± SEM	*n*	%	Mean ± SEM	
Age in years			29.52 ± 0.92			29.70 ± 0.90	0.890
18–25	34	37.78		40	44.44		
26–35	36	40.00		31	34.44		
36–45	14	15.56		14	15.56		
46–60	6	6.66		5	5.56		
Sex							0.999
Male	42	46.67		43	47.78		
Female	48	53.33		47	52.22		
Marital status							0.549
Married	51	56.67		46	51.11		
Unmarried	39	43.33		44	48.89		
BMI (kg/m^2)			23.3 ± 0.44			23.63 ± 0.42	0.581
Below 18.5	11	12.22		7	7.78		
18.5–25.0	50	55.56		56	62.22		
Above 25.0	29	32.22		27	30		
Education level							0.150
Illiterate	4	4.44		4	4.44		
Primary	13	14.44		6	6.67		
Secondary	43	47.78		59	65.56		
Graduate/above	30	33.34		21	23.33		
Occupation							0.366
Housewife	16	17.78		15	16.67		
Employed	44	48.89		36	40.00		
Unemployed	30	33.33		39	43.33		
Economic Impression							0.985
Low	29	32.22		30	33.33		
Medium	43	47.78		42	46.67		
High	18	20.00		18	20.00		
Smoking History							0.999
Smoker	8	8.89		7	7.78		
Non-smoker	82	91.11		83	92.22		
Residence Area							0.650
Rural	40	44.44		36	40.00		
Urban	50	55.56		54	60.00		
Previous History							**< 0.001**
Yes	13	14.44		0	0.00		
No	77	85.56		90	100.00		
Family History							0.063
Yes	12	13.33		4	4.44		
No	78	86.67		86	95.56		

Abbreviations: OCD, obsessive compulsive disorder; SEM, standard error mean; BMI, body mass index; DSM-5, Diagnostic and Statistical Manual of Mental Disorders (5th Edition); Y-BOCS, Yale-Brown Obsessive-compulsive Scale. Significant p-values are in bold

(Val158Met) among OCD cases revealed frequencies of 54.44% for GG, 38.89% for GA, and 6.67% for AA, whereas the respective frequencies within the control group were 76.67%, 21.11%, and 2.22%. A statistically notable association was observed with the GA genotype and increased OCD risk with odds ratio of 2.59 (95% CI: 1.33–5.06; $p=0.005$). Although AA genotype demonstrated a higher estimated risk (OR = 4.22, 95% CI: 0.81–21.81), this result failed to achieve statistical significance ($p=0.085$). In the dominant genetic model (GA + AA vs. GG), the association persisted as significant with an odds ratio of 2.75 (95% CI: 1.45–5.22; $p=0.002$), suggesting that carriers of at least one A allele are at greater risk. However, analysis under the recessive model (AA vs. GG + GA) did not reveal a notable relationship (OR = 3.15, 95% CI: 0.62–16.01; $p=0.168$). At the allelic level, the prevalence of the A allele was elevated in OCD group (26.11%) compared to controls (12.78%), and this

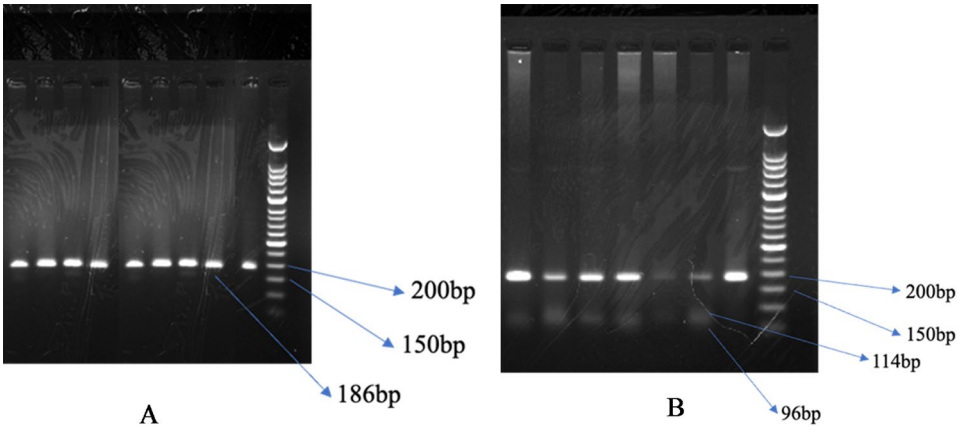

Fig. 1 Representative agarose gel electrophoresis images of PCR-RFLP products for COMT rs4680 genotyping. A 50 bp DNA ladder was used as the molecular size marker. (**A**) Representative gel image of PCR products showing the major visible band at 186 bp. (**B**) Additional representative gel image of digested PCR products obtained under the same electrophoresis conditions. Because the 96 bp and 114 bp fragments are closely spaced in size, their separation was limited under the gel conditions used, and the smaller 18 bp, 32 bp, and 40 bp fragments were not resolved

Table 3 *COMT* rs4680 genotype frequency and Hardy-Weinberg equilibrium analysis

Allele	OCD Patients			HWE		Controls			HWE	
	Male, *N* = 45	Female, *N* = 45	Total, *N* = 90	χ^2	*p*	Male, *N* = 42	Female, *N* = 48	Total, *N* = 90	χ^2	*p*
GG	26	23	49	0.01	0.941	32	37	69	0.25	0.616
GA	17	18	35			9	10	19		
AA	2	4	6			1	1	2		

Abbreviations: HWE, Hardy-Weinberg equilibrium; OCD, obsessive compulsive disorder; OR, odds ratio. p-value > 0.05 obeyed Hardy-Weinberg equilibrium

Table 4 Allele and genotype frequencies of the *COMT* rs4680 polymorphism in both cases and controls

COMT, rs4680	Case (*n* = 90)	Control (*n* = 90)	OR (95% CI)	*p*-value
GG	49 (54.44)	69 (76.67)	1	
Heterozygote model (GA vs. GG)	35 (38.89)	19 (21.11)	2.59 (1.33 to 5.06)	**0.005**
Homozygote model (AA vs. GG)	6 (6.67)	2 (2.22)	4.22 (0.81 to 21.81)	0.085
Dominant model (GA + AA vs. GG)			2.75 (1.45 to 5.22)	**0.002**
Recessive model (AA vs. GG + GA)			3.15 (0.62 to 16.01)	0.168
G	133 (73.89)	157 (87.22)		
A	47 (26.11)	23 (12.78)		
Allelic model (A vs. G)			2.41 (1.39 to 4.18)	**0.002**

Values are expressed as no. (%). $P < 0.05$ is considered as significant

difference was found out to be statistically significant, with an OR of 2.41 (95% CI: 1.39–4.18; $p = 0.002$), indicating that carrying the A allele may confer increased susceptibility to OCD. The odds ratios and 95% confidence intervals for the different genetic models are also illustrated in Fig. 2.

In Tables 5 and 6 the comparison within the male and female subsamples of the *COMT* rs4680 (Val158Met) polymorphism reveals some important differences. In males, the GG genotype was more common in controls (76.19%) than in cases (57.78%), while in females, this genotype was similarly higher in controls (77.08%) but lower in cases (51.11%). The GA genotype, however, showed a notable difference between genders. Males exhibited a higher frequency of GA in cases (37.78%) versus controls (21.43%) but this difference did not show statistical significance (OR = 2.3 3, 95% CI: 0.89–6.07; $p = 0.084$), while females showed a much more significant difference, with GA being present in 40% of cases versus 20.83% in controls (OR = 2.89, 95% CI: 1.14–7.35; $p = 0.025$). In case of AA genotype frequency, no statistically significant association was observed in any of the subgroups. Moreover, the dominant model (GA + AA vs. GG) suggested a stronger association in females (OR = 3.22, 95% CI: 1.32–7.85; $p = 0.010$) than in males (OR = 2.34, 95% CI: 0.93–5.89; $p = 0.072$). Furthermore, the A allele was significantly linked with the condition in females (OR = 2.84, 95% CI: 1.33–6.06; $p = 0.007$), whereas the association was weaker and not significant in males (OR = 2.02, 95% CI: 0.91–4.49; $p = 0.085$).

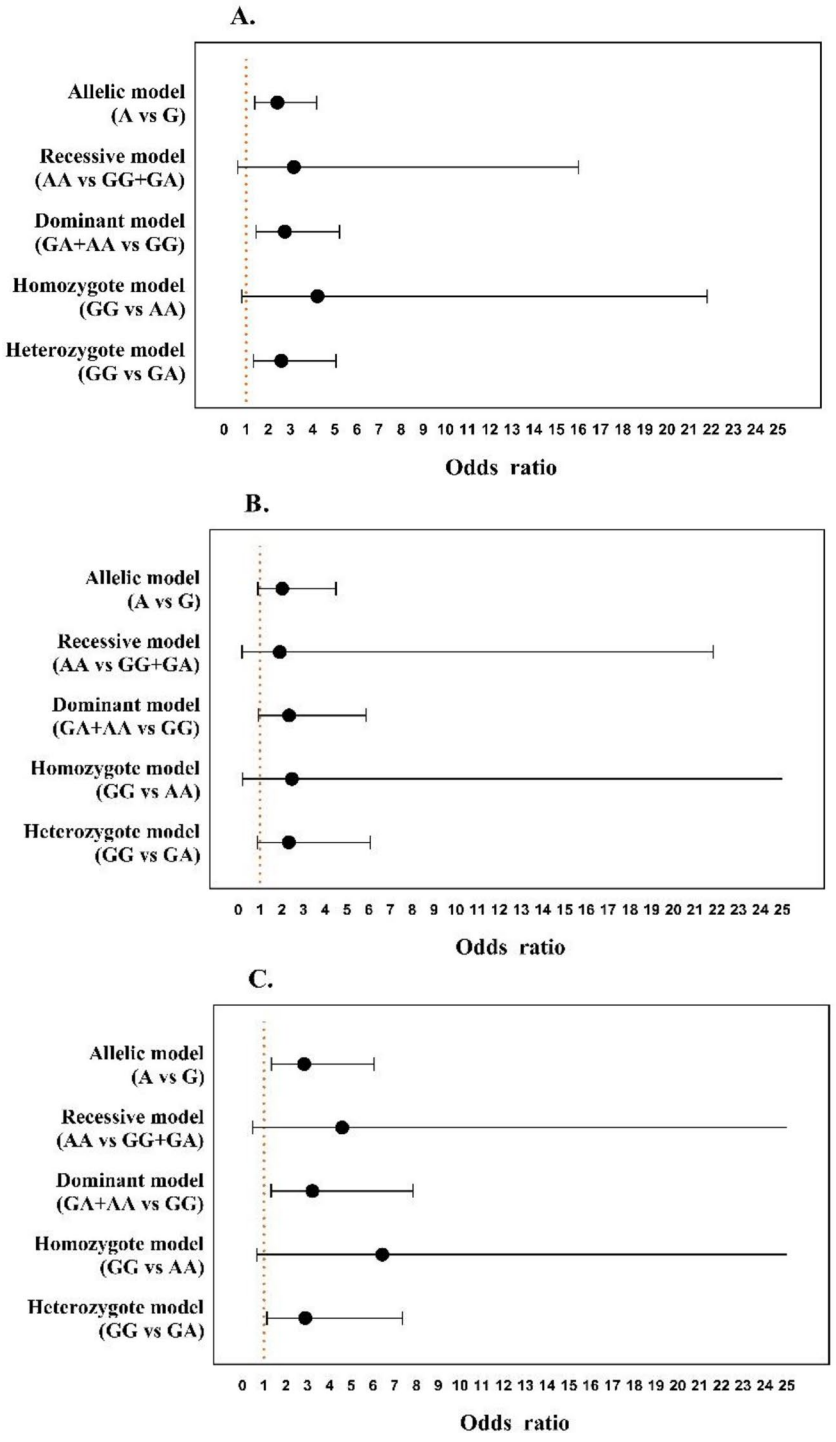

Fig. 2 Forest plot showing odds ratios (ORs) and 95% confidence intervals (CIs) for the association between *COMT* rs4680 and OCD under different genetic models. (**A**) Total study population; (**B**) Male subgroup (**C**) Female subgroup

4 Discussion

OCD is a common, persistent condition that is both costly and debilitating, and it is seldom accurately diagnosed or treated [1]. Although the exact cause of OCD is still unknown, several contributing factors have been identified. Family and genetic studies have consistently shown that genetic factors significantly contribute to the development of OCD. A well-established genetic predisposition makes a family history of the disorder a major risk factor [36]. Furthermore, OCD is characterized by a notable risk of recurrence, even when treatment has been effective. A longitudinal study of 213 people diagnosed

Table 5 Allele and genotype frequencies of the *COMT* rs4680 polymorphism within the male subsamples of the cases and controls

COMT, rs4680	Case ($n=45$)	Control ($n=42$)	OR (95% CI)	*p*-value
GG	26 (57.78)	32 (76.19)	1	
Heterozygote model (GA vs. GG)	17 (37.78)	9 (21.43)	2.33 (0.89 to 6.07)	0.084
Homozygote model (AA vs. GG)	2 (4.44)	1 (2.38)	2.46 (0.21 to 28.69)	0.472
Dominant model (GA + AA vs. GG)			2.34 (0.93 to 5.89)	0.072
Recessive model (AA vs. GG + GA)			1.91 (0.17 to 21.84)	0.604
G	69 (76.67)	73 (86.91)		
A	21 (23.33)	11 (13.09)		
Allelic model (A vs. G)			2.02 (0.91 to 4.49)	0.085

Values are expressed as No. (%). $P<0.05$ is considered as significant

Table 6 Allele and genotype frequencies of the *COMT* rs4680 polymorphism within the female subsamples of the cases and controls

COMT, rs4680	Case ($n=45$)	Control ($n=48$)	OR (95% CI)	*p*-value
GG	23 (51.11)	37 (77.08)	1	
Heterozygote model (GG vs. GA	18 (40.0)	10 (20.83)	2.89 (1.14 to 7.35)	**0.025**
Homozygote model (GG vs. AA)	4 (8.89)	1 (2.09)	6.43 (0.68 to 61.19)	0.105
Dominant model (GA + AA vs. GG)			3.22 (1.32 to 7.85)	**0.010**
Recessive model (AA vs. GG + GA)			4.59 (0.49 to 42.69)	0.181
G	64 (71.11)	84 (87.50)		
A	26 (28.89)	12 (12.50)		
Allelic model (A vs. G)			2.84 (1.33 to 6.06)	**0.007**

Frequencies are expressed as no. (%). $P<0.05$ is considered as significant. Abbreviations: OR: odds ratio

with OCD over five years revealed that 59% of those who achieved recovery subsequently experienced a relapse [37].

In our study, symptom recurrence was observed in 14.44% of the cases consistent with the recurrent nature of the disorder. The family history of OCD did not play a statistically significant role but a near-significant difference (Table 2, $p=0.0639$) in family history of OCD further suggests a potential hereditary influence. Significant differences in the DSM-5 and Y -BOCS scores across the two study groups ($p<0.001$) demonstrate the successful implementation of the study's inclusion criteria. The elevated scores in the case group confirm point to notable obsessive-compulsive symptoms, while the minimal scores in the control group validate their healthy status. This robust differentiation between the two groups, using established diagnostic and severity measures, strengthens the internal validity of the study. Moreover, the two groups were well-matched on key baseline demographic variables including age, gender, marital status, education, economic condition, occupation, BMI, smoking history, and residence area as no statistically noteworthy differences were found across these variables (Table 2, $p>0.05$). This careful matching minimizes the potential for confounding effects in subsequent genetic analyses.

Studies into families and genetics have long indicated that genetic influences are key to the development of OCD [38–40]. One of the most studied genetic factors for psychiatric disorders is *COMT* rs4680 (G to A) polymorphism [41]. The Val (G) allele is related to enhanced enzymatic function, leading to lower synaptic dopamine concentration, while the Met (A) allele results in reduced enzyme function with greater dopamine availability, particularly in the prefrontal cortex [41]. This particular polymorphism has been extensively investigated for its association with psychiatric disorders, including schizophrenia, anxiety, bipolar disorder, depression, and OCD [42–46]. Although there are numerous studies in this regard, the findings are often conflicting. A pooled analysis of 14 case-control studies comprising 1,435 individuals with OCD and 2,753 healthy controls found a significant association between the *COMT* Val158Met polymorphism and OCD risk. Statistically significant associations appeared in the allele contrast (OR = 1.14, $p=0.01$), homozygote (OR = 1.33, $p=0.004$), and dominant (OR = 1.14, $p=0.04$) models [47]. Another Japanese case-control study (171 OCD cases, 944 controls) observed no significant link between the polymorphism and OCD risk or treatment response. The presence of the Met al.lele did not predict either outcome ($p>0.05$) [48].

In our study, the GA heterozygous genotype was associated with a 2.59-fold greater risk of developing OCD relative to the GG common homozygous genotype, with a statistically significant association between them (Table 4, $p=0.005$). The AA genotype showed a 4.22-fold higher risk, though the association failed to achieve notable statistical significance (Table 4, $p=0.085$). In the dominant model (GA + AA vs. G G) a statistically significant association was observed (Table 4, $p=0.002$). In contrast, the recessive model (AA vs. G G + GA) indicated a higher

risk for the AA genotype, but without statistical significance (Table 4, $p = 0.168$). The A allele was further correlated with an elevated risk of OCD in the allele contrast model (Table 4, OR = 2.41, $p = 0.002$), aligning with previous reports, although the strength of association varied by subgroup [46]. In our gender-stratified analysis, the associations in females were more pronounced compared to men. Among males, the risk increase (OR = 2.33) did not achieve statistical significance (Table 5, $p = 0.084$) whereas in females, the GA genotype conferred a 2.89-fold increased risk (Table 6, $p = 0.025$). In the dominant genetic model (GA + AA vs. G G), male carriers exhibited a 2.34-fold increased risk of OCD which did not reach statistical significance (Table 5, $p = 0.072$). In contrast, female carriers demonstrated a statistically significant association exhibiting a 3.22-fold higher risk (Table 6, $p = 0.01$). Similarly, male carriers of the A allele had a 2.02-fold higher risk which was not statistically significant (Table 5, $p = 0.085$), whereas female carriers displayed a significant 2.84-fold elevated risk of developing OCD (Table 6, $p = 0.007$).

In case of female subgroup, our findings replicate the results of a similar study on Afrikaner population where GA genotype was significantly more prevalent in female OCD cases than female controls ($p = 0.029$) [49]. In males, that study reported a significant association between the GA genotype and OCD ($p = 0.043$), which contrasts with our findings. Moreover, comparing our results to a study conducted in southern England, notable differences emerge in the gender-specific associations of the COMT gene with OCD. That study, which included 87 OCD patients and 327 healthy Caucasian controls, found a significant association only in males. Specifically, men carrying the Met158 allele had a 1.91-fold increased risk of OCD (OR = 1.91, $p = 0.026$), whereas no meaningful association was detected in females (OR = 1.13, $p > 0.05$) [50]. Our study improves upon existing research by using a well-defined Bangladeshi cohort, incorporating gender-stratified analysis, and applying five different genetic models to identify associations often overlooked in broader meta-analyses. These findings can contribute to clinical practice by guiding population-specific genetic screening for OCD risk, informing personalized treatment strategies, and aiding in early identification of high-risk subgroups, particularly females carrying the A allele.

Despite these promising findings, several limitations should be acknowledged. Our study featured a relatively modest sample size and lacked longitudinal follow-up data, which may restrict the generalizability and depth of the conclusions. The limited sample size is partly because participants were recruited over a six-month period under strict inclusion and exclusion criteria, which narrowed the eligible sample. Another limitation is that genotyping accuracy was not independently validated through methods such as Sanger sequencing or duplicate laboratory assays. Although standard PCR-RFLP procedures were followed, the absence of an external validation step may leave room for undetected genotyping errors. Moreover, because multiple genetic models and subgroup analyses were conducted without correction for multiple testing, adjustment for potential confounders or formal interaction testing, there is an increased risk of Type I error that may overestimate the significance of some associations. Therefore, these results should be considered exploratory rather than confirmatory. Additionally, analyses of gene–gene interactions were not performed, limiting insight into potential synergistic genetic effects. Although this is the first investigation of this SNP within the Bangladeshi population, the variant itself is not novel and has been examined extensively in other populations. Because rs4680 is a common functional variant with expected small effect sizes, the present findings should be interpreted as exploratory evidence of association rather than proof of causality. Further validation through larger studies, meta-analysis of multiple datasets, and functional studies are needed to confirm these results and understand the underlying mechanisms.

5 Conclusion

Ours is the first study to explore the association between the *COMT* rs4680 polymorphism with OCD in a Bangladeshi cohort, offering new insights into genetic vulnerability within this ethnic group. We observed a higher frequency of the GA genotype among individuals with OCD, particularly among females, suggesting possible gender-specific genetic effects. Although these findings indicate the possible role of *COMT* variation in OCD susceptibility, these results should be interpreted carefully given the modest sample size. Future studies should aim to validate these findings in larger and more ethnically diverse populations, along with functional analyses and evaluation of additional genetic markers. Despite the limitations, our research contributes valuable initial data from an underrepresented population and emphasizes the importance of continued research into genetic factors that may influence OCD risk.

Abbreviations

BMU	Bangladesh Medical University
CI	Confidence interval
COMT	Catechol-O-methyltransferase
DNA	Deoxyribose nucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
HCs	Healthy controls
MDD	Major depressive disorder
OCD	Obsessive-compulsive disorder
OR	Odds ratio
PCR-RFLP	Polymerase chain reaction–restriction fragment length polymorphism
PFC	Prefrontal cortex
ROC	Receiver-operating characteristic

SEM	Standard error mean
SPSS	Statistical package for social sciences
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale

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Author contributions
A.N.R., M.G., M.R.I., and Z.N.: conceptualization, methodology, data curation, formal analysis, and writing-original draft. M.M.A.S.Q., M.S., and M.A.B.: data curation, investigation, and project administration. M.R.I. and Z.N.: supervision, and writing review, editing & revision.

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Data availability
The datasets generated and analyzed during this research are available from the corresponding author upon rational request.

Declarations

Ethical approval
This study was approved by the Research Ethics Committee, University of Asia Pacific (Ref: UAP/REC/2024/116). Before the commencement of data collection, we ensured the individuals were aware of the purpose of this study and then written informed consent forms were acquired. The study was carried out in accordance with the principles mentioned Declaration of Helsinki.

Human ethics and consent to participate
All participants provided written informed consent prior to enrollment. Informed consent for the publication is not applicable to this study.

Competing interests
The authors declare no competing interests.

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