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DNA SEQUENCING, MUTATIONAL ANALYSIS OF NOVEL COMT GENE VARIANTS AND ITS PATHOGENICITY IN SCHIZOPHRENIA PATIENTS: ACROSS-SECTIONAL STUDY FROM TUMKUR DISTRICT OF SOUTH KARNATAKA

Ramesh Babu Elle [*1], S. R. Bulagouda [2], Santhosh Kumar Nune [3] and Bavana [4]

Department of Anatomy [1], B. L. D. E. University, Vijayapura - 586103, Karnataka, India.
Department of Anatomy [2], Department of Psychiatric [3], Shridevi Institutes of Medical Sciences & Research Hospital Tumkur - 572106, Karnataka, India.
Department of Biochemistry [4], Prathima Relief Institute of Medical Sciences, Warangal - 506006, Telangana, India.

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Correspondence to Author:
Ramesh Babu Elle

Tutor,
Department of Anatomy,
B. L. D. E. University, Vijayapura - 586103, Karnataka, India.

E-mail:ramesh.eanatomy@gmail.com

ABSTRACT: Introduction: Schizophrenia is a multi-factorial neuropsychiatric disorder, influenced by environmental and genetic factors. The catechol-O-methyltransferase (COMT) gene is a crucial for the metabolism of dopamine. It has been thoroughly investigated for its potential role in SCZ. At the same time; several variants in the COMT gene have been reported in diverse populations in South Karnataka but remain unexplored. **Aim:** To assess the novel variants related to the COMT gene and their correlation with SCZ symptoms and other health issues in patients. **Materials and Methods:** The study was carried out on 80 patients aged between 18 and 60 years; the results were compared with healthy controls of 80. The samples of blood were collected for the DNA extraction. PCR was used to amplify the COMT gene, followed by sequencing to identify variants. Standardized scales were used for gauging the severity of the symptoms. **Results:** Two novel changes in a single nucleotide (SNPs) (non-synonymous) were identified in the COMT gene in exon -4 of two female SCZ patients out of 80 patients are exon 4: c.449A>T [Gln150Leu] and c.114G>C [p. Ala123Pro]. The c.449A>T [Gln150Leu] variant was associated with paranoid-type positive symptoms, while c.114G>C [p. Ala123Pro] was associated with catatonic-type positive symptoms, while their challenging other symptoms like as pre-menopausal, obesity and endocrine symptoms would have an adverse effect on their lifestyle activity. **Conclusion:** In this study results identified novel COMT gene variants linked with specific symptomatology in SCZ patients' variants that may contribute to the phenotypic abnormalities notified in SCZ. Further study with larger cohorts is needed to validate these findings and explore their influence on customized therapies.

INTRODUCTION: Schizophrenia (SCZ) is a persistent and severe psychological condition that compromises thought the processes, perception, emotional regulation, and behaviour.

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It impacts nearly 1% of the world population, with symptoms often emerging in early adulthood or late adolescence [1].

This disorder is a high degree of clinical heterogeneity, with positive (+) symptoms of delusions, hallucinations, & rambling speech and negative (-) symptoms of anhedonia, apathy, and social disengagement and also cognitive dysfunction like impaired executive functioning, memory (working) deficits [2]. Despite decades of studies, the precise etiology of SCZ remains

unclear, but it is widely recognized as a multifactorial disorder connecting a complicated relationship between neurobiological, genetic, and environmental factors [2, 3]. Among the various risk aspects, genetic predisposition plays a major part in SCZ susceptibility. Many studies reported that 60–80% of SCZ risk is attributable to genetic factors, with heritability rates comparable to other highly genetic symptoms like autism spectrum disorder and bipolar disorder [4]. Numerous potential genes have been implicated in SCZ, including *DISC1, NRG1, DRD2,* and *COMT* are involved in glutamatergic and dopaminergic neurotransmission [5, 6]. The *COMT* gene is an accountable for the degradation of catecholamines such as norepinephrine, dopamine, and epinephrine [7]. Dopamine dysregulation, particularly in the PFC, or prefrontal cortex and striatum, have been significantly implicated in the pathophysiology of SCZ [8]. The enzyme *COMT* plays an essential role in moderating dopamine levels in the PFC, which is fortified for executive function, cognitive flexibility, and working memory [9]. Gene variants& their novel variants adverse effect on human healthy life cycle such as lifestyle modifications such as lack of interest in social activities, habits, daily activities, and physical activity [10]. The COMT gene is crucial for its potential role in SCZ, while several variants in the COMT gene have been reported in diverse populations in South Karnataka but still remains unexplored. The focus of this study is to assess a novel variant related to the COMT gene and their correlation with SCZ symptoms in patients.

MATERIAL AND METHODS: Eighty individuals diagnosed with SCZ patients and eighty healthy subjects ages between 18 and 60 years were registered in this study. This study was conducted as a cross-sectional observational study from 2023 to 2024, who underwent treatment in outpatient department (OPD) of psychiatry in Shridevi Institute of Medical Sciences and Research Hospital, Tumkur, Karnataka were included after taking the inform consent from the patients and the study was approved by the institutional ethical committee Overseeing human studies (with reference number SIMS & RH/SRC/2023012). Strict adherence to ethical standards was maintained to ensure patient safety, confidentiality and voluntary participation.

The attendees were opted depending on the following criteria: aged between 18 and 60 years to include both early and late-onset SCZ cases; regular follow-up patients at the tertiary care hospital, ensuring consistent medical supervision; and capability to offer informed consent, or consent obtained from a legally authorized representative if required.

Inclusion and Exclusion Criteria: The following totality were excluded from the study: patients with bipolar disorder or deadly depressive disorder, concurrently mental illnesses, to avoid genetic overlap; individuals with a history of neurological illnesses, like traumatic brain injury, epilepsy, or neurodegenerative disorders; individuals having a history of substance use disorder, as substance-induced psychosis could confound the results; pregnant and lactating women, to minimize confounding physiological variations in hormonal levels affecting dopamine metabolism; and individuals unwilling to provide informed consent or people who are unable to give legal consent due to significant cognitive impairment.

DNA Isolation: To investigate novel variants of the gene of COMT in SCZ patients, the investigation's subjects' samples of the peripheral blood went through testing to get genomic DNA. The overall amount of 3 mL of full of blood was collected from the median cubital vein of each of the 60 SCZ patients under strict aseptic conditions. The blood was handed over swiftly, into 4 mL EDTA-coated tubes to minimize coagulation and assure a long-term stability of nucleic acids. After being collected, every blood sample were stored at -80°C to preserve DNA integrity and prevent degradation prior to extraction. Acquisition of genomic DNA from 250 µL of whole blood using the G. Bio Science Kit method, following the manufacturer’s protocol. The perfection and quantity of extracted DNA were assessed using Nanodrop spectrophotometry (USA: Thermo Fisher Scientific Inc.) by measuring the 260/280 nm absorbance ratio to confirm DNA purity. Additionally, the substance of agarose gel electrophoresis (1% gel, ethidium bromide-stained) was performed to evaluate DNA integrity. Only samples with high-quality, intact DNA were used for adherent analyses.

DNA Amplification and PCR Conditions: To amplify the desired area of the COMT gene (exon 4), specific primers were designed using Primer 3 software tools, based on the reference Genomic Accession Number: NG_011526 (NCBI Reference Sequence Database). The forward and reverse primer sequences used for amplification were: Forward primer (F'): 5'-GTTCCCCTCTCTCCACCT-3' and Reverse primer (R'): 3'-GTCTTTCCTCAGCCCCAG-5'. The total PCR reaction mixture (25 µL) was prepared as follows:1.5 µL Forward Primer; 1.5 µL Reverse Primer; 10.8 µL Nuclease-free water (H_2O); 15.5 µL PCR Master Mix (including Taq polymerase, dNTPs, MgCl, and buffer); and 1–2 µL Genomic DNA template.

TABLE 1: PCR AMPLIFICATION USING A THERMAL CYCLER (APPLIED BIOSYSTEMS VERITI 96-WELL PCR SYSTEM)

Step	Time	Temperature (°C)	Cycles
Initial Denaturation	5 min	95°C	1 cycle
Denaturation	30 sec	94°C	35 cycles
Annealing	30 sec	55°C	35 cycles
Extension	45 sec	72°C	35 cycles
Final Extension	5 min	72°C	1 cycle
Hold		4°C	-

PCR amplification was performed using a Thermal Cycler (Applied Bio systems Veriti 96-Well PCR System) conditions as shown in **Table 1**. The PCR products were visualized using agarose gel electrophoresis (1.5 % gel, stained with ethidium bromide) under a UV transilluminator (Bio-Rad, USA) to confirm successful amplification.

Sequencing and Mutation Analysis: Sequencing was performed byusing an ABI 3730xl DNA Analyzer (Applied Biosystems, USA) following the manufacturer's protocols. The sequencing data were analyzed using MEGA version 7.0 software and aligned against the NCBI reference sequence. Mutational analysis was conducted by comparing the obtained sequences with the wild-type *COMT* gene sequence from NCBI.

***In-silico* Analysis for Variant Prediction and Pathogenicity:** To determine the pathogenicity of novel *COMT* gene variants, Algorithmic forecasts were performed using multiple *in-silico* tools, including: SIFT (Scale-Invariant Feature Transform), predicts if an amino acid transformation impacts protein function; PolyPhen-2 (Polymorphism Phenotyping v2), evaluates the potential deleterious impact of mutations based on structural and functional effects; Mutation Taster, analyses the likelihood of mutations being disease-causing or neutral based on comparative genomics; and FATHMM (Functional Analysis through Hidden Markov Models), assesses the functional consequences of mutations in protein-coding genes. The identified mutations were further categorized following the ACMG (American College of Medical Genetics and Genomics) and the AMP (Association for Molecular Pathology) criteria [11]. The variants were categorized into likely pathogenic, pathogenic, benign, and likely benign, and variant of uncertain significance (VUS).

Statistical Analysis: The statistical analysis was carried out by using the SPSS (Statistical Package for Social Sciences) software. The Fisher test was applied for the statistical analysis and the results were expressed P values ($p < 0.001$) were considered as highly significant.

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RESULTS:

TABLE 2: IDENTIFICATION OF NOVEL VARIANTS FREQUENCIES IN CASE AND CONTROLS GROUPS

Novel genotype	Case[n=80]	Control [n=80]
A/T	Male-0/35 female-1/45	Nil
G/C	Male:0/35 female:2/45	Nil

Identification of Novel Variant Frequencies results presents the frequency of newly identified genetic variants in both case and control groups. The A/T and G/C genotypes were observed exclusively in female cases, but were absent in the control group.

Specifically: The A/T genotype was found in one female case but was not present in males or the control group. The G/C genotype was identified in two female cases but was absent in males and controls. This suggests a potential association between these novel genetic variants and the studied condition, particularly in females **Table 2**.

TABLE 3: TO NOVEL MUTATION ASSOCIATED WITH NON-SCHIZOPHRENIA SYMPTOMS & INFLUENCE ON DAILY ACTIVITIES

Novel mutations	Symptoms	Life style implications
A/T	Menstrual compliances & Hormonal fluctuations.	Lack of hungriness, Decrease sexual drive, Chronic symptom and Infertility issue.
G/C	Irregular periods, BMR and Hormonal issues.	Not interest in social activities, Unable to eat food, Lack of interest other activity, Lack of sexual drive, Mood swings and Chronic symptoms.

The A/T genotype is linked to endocrine abnormalities, premenstrual symptoms, malnutrition, infertility, and reduced sexual drive. The G/C genotype is associated with endocrine issues, obesity, and lack of social engagement, reduced food interest, and diminished sexual drive. The findings highlight a significant impact of these genetic variants on female health and daily life. The study suggests that novel missensemutations identified in female schizophrenia (SCZ) patients, specifically in Tumkur district, could contribute to adverse health effects and lifestyle difficulties **Table 3.**

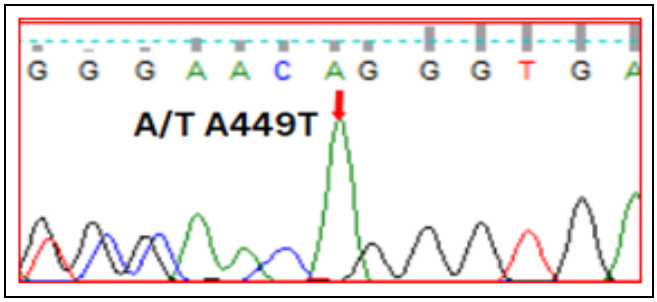

FIG. 1: IDENTIFICATION OF NOVEL MUTATION IN COMT GENE EXON: 4, A/ T

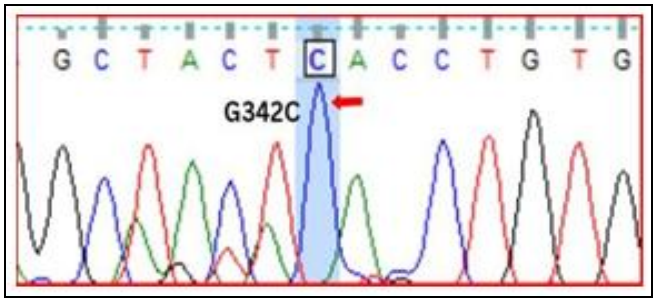

FIG. 2: IDENTIFICATION OF NOVEL MUTATIONS IN COMT GENE EXON: 4, G/C

Fig. 1 & 2 illustrates that, the identified missense novel variants is c.449A>T (p. Gln150Leu) and c.114G>C (p. Ala123Pro), in exon 4 of the *COMT* gene, as detected through Sanger sequencing. The sequencing chromatogram confirms the presence of these nucleotide substitutions, which result in amino acid changes affecting protein function. Further genotype-phenotype correlation analysis revealed that a 38-year-old female SCZ patient carried the c.449A>T (p. Gln150Leu) variant, with corresponding clinical manifestations consistent with paranoid SCZ. In this study, two novel unreported missense mutations in exon 4 of the *COMT* gene were identified in two female SCZ patients from Tumkur, South Karnataka, India. These novel SNPs werec.449A>T (p. Gln150Leu), a non-synonymous mutation substituting glutamine (Q) with leucine (L) at position 150 of the *COMT* protein and c.114G>C (p. Ala123Pro), a non-synonymous mutation replacing alanine (A) with proline (P) at position 123 of the *COMT*protein. Till date these mutations were not reported in global databases such as *ClinVar* or *dbSNP*, confirming their novelty.

TABLE 4: PATHOGENICITY PREDICTION SCORES OF NOVEL *COMT* VARIANTS

Variant	Amino acid	Nucleotide	Exon-4	SIFT Score	PolyPhen-2 Score	Mutation Taster Score	FATHMM Score	ACMG Classification
c.449A>T (p. Gln150Leu)	Gln/ Leu	A>T	4	0.018 (damaging)	0.03 (benign)	0.914 (disease-causing)	-0.51	Pathogenic
c.114G>C (p. Ala123Pro)	Ala/ Pro	G>C	4	0.007 (damaging)	0.98 (probably damaging)	0.999 (disease-causing)	-0.92	Pathogenic

Prediction score: SIFT score: 0-1, Polyphen-2 score = >0.908probablydamaged, Mutation taster (0.0-215). [mutation taster organization), proven, Fatham.

In-silico pathogenicity predictions used to assess the beneficial significance of these new mutations, bioinformatics tools were used, including SIFT, PolyPhen-2, Mutation Taster, and FATHMM. Both variants were classified as pathogenic based on ACMG/AMP criteria [12]. The c.114G>C (p. Ala123Pro) mutation was anticipated to have a more severe functional impact than c.449A>T (p. Gln150Leu) due to higher PolyPhen-2 and Mutation Taster scores **Table 4**.

TABLE 5: CLINICAL SYMPTOMS ASSOCIATED WITH NOVEL *COMT* VARIANT

Novel COMT variant	Genotype	Exon	Positive Symptoms	Negative Symptoms	Cognitive Symptoms	General Symptoms
c.449 A >T (p. Gln 150 Leu)	A>T	4	Paranoid symptoms	None	None	None
c.114 G > C (p. Ala 123 Pro)	G>C	4	Catatonic symptoms	None	None	None

Genotype-Phenotype Correlation of each novel *COMT* variant was linked with specific SCZ symptomatology, as showed in **Table 5**. The first novel COMT variant is c.449A>T (p. Gln150Leu) mutation was identified in a 38-year-old female sample, who presented with paranoid SCZ symptoms, including delusions, persecutory thoughts, and auditory hallucinations. The second novel COMT variant is c.114G>C (p. Ala123Pro) mutation was identified in a 45-year-old female patient, who exhibited catatonic SCZ symptoms, characterized by posturing, grimacing, motor rigidity, and hyperactivity.

TABLE 6: **CORRELATION OF C.254A>T AND C.114 G>C CLINICAL SYMPTOMS IN SCZ SAMPLE**

Genotype	Protein	Symptoms	Characterization
A>T	p. Gln150L	General Symptoms	Tension and sleeping
		Positive symptoms	Disorganized speech
G>C	p. Ala123Pro	General symptoms	Somatic concern & Poor attribute.
		Positive symptoms	Posturing, grimacing, mannerisms, performing, stereotype & hyperactivity

The genotype-phenotype correlation analysis revealed unique clinical manifestations correlated withthe identified novel *COMT* gene variants. The c.449A>T (p. Gln150Leu) mutation was predominantly linked to general symptoms such as tension and sleep disturbances, along with positive symptoms like disorganized speech. Conversely, the c.114G>C (p. Ala123Pro) mutation exhibited a stronger association with catatonic SCZ, characterized by general symptoms including somatic concerns and poor attribution, alongside positive symptoms such as posturing, grimacing, stereotyped behaviors, and hyperactivity. These findings indicate a potential role of these novel mutations in the modulation of dopaminergic neurotransmission, influencing SCZ symptomatology **Table 6**.

DISCUSSION: SCZ risk is a multifactorialbehavioural illnessdisorder with a problematic interplay of genetic, neurochemical, and environmental factors influencing its pathophysiology. Among the various candidate genes implicated in SCZ, the *COMT* gene, located on chromosome 22q11.21, has been extensively studied due to its crucial role in dopaminergic neurotransmission. The enzyme encoded by *COMT* is responsible for degrading catecholamines, particularly dopamine, in the PFC, a brain region associated with executive functions, emotional regulation, and working memory [13]. Given that dopamine dysregulation is a well-established hallmark of SCZ, *COMT* gene variants have been suggested to contribute to the variability in SCZ symptoms and disease [14, 15]. Research on genetics has discovered important heterogeneity in SCZ susceptibility across different ethnic and geographic populations. GWAS investigations of Genome-wide associations have found over 100 SCZ-associated loci, but the effects of these loci vary among population [16].

Studies in Caucasian populations have emphasized the purpose of the *COMT Val158Met* variant, whereas research in Asian and African populations suggests the presence of additional, less-characterized variants that may play a significant role in SCZ pathophysiology [17]. A research conducted byon North Indian SCZ patients found significant relations between COMT polymorphisms and symptom severity, particularly in paranoid SCZ [18].

However, data from South India, particularly Karnataka, is scarce. Given the distinct genetic background of South Indian populations, studying novel *COMT* variants in SCZ patients from Tumkur district, South Karnataka might provide crucial details about the disorder's regional genome-wide architecture. Tumkur district, located in South Karnataka, India, has a unique genetic pool influenced by local ancestry, dietary habits, and environmental factors. Whilst an abundance of analysis has cantered on the north Indian genetic landscape, south Indian populations remain underrepresented in psychiatric genetics research [19].

Two new missense mutations were found in the current investigationin exon: 4 of the *COMT* gene, c.449A>T (p. Gln150Leu) and c.114G>C (p. Ala123Pro), in SCZ patients from Tumkur district, South Karnataka. These variants were classified as pathogenic using *in-silico* bioinformatics tools, with c.449A>T associated with paranoid SCZ symptoms and c.114G>C linked to catatonic SCZ symptoms. The functional impact of these mutations likely arises from alterations in *COMT* enzymatic activity, which in turn affects dopamine metabolism. Prior research has mostly examinedon the Val158Met (rs4680) polymorphism, which influences COMT enzyme stability and has been linked to cognitive impairments and psychotic symptoms [20-22].

However, the current study provides novel proof that additional rare or novel COMT mutations may play a role in modulating dopaminergic function and SCZ symptomatology. The c. 449A>T (p. Gln150Leu) mutation involves a substitution of glutamine (Q) with leucine (L) at position 150 of the COMT protein. This mutation was reported in a 38-year-aged old female patient diagnosed with paranoid SCZ, exhibiting delusions, persecutory thoughts, and auditory hallucinations. Paranoid SCZ has been linked with hyperdopaminergic activity in the mesolimbic pathway, suggesting that this mutation may contribute to an overactive dopamine system, increasing susceptibility to positive symptoms such as hallucinations and delusion [23]. Additionally, computational pathogenicity analysis classified this variant as damaging, indicating its potential role in altering *COMT* enzymatic function.

Conversely, the c.114G>C (p. Ala123Pro) mutation, which leads to the substitution of alanine (A) with proline (P) at position 123, was detected in a 45-year-aged old female patient diagnosed with catatonic SCZ. Catatonia is characterized by motor disturbances, including posturing, grimacing, repetitive movements, and psychomotor rigidity, symptoms often linked to dopaminergic hypoactivity in the basal ganglia [24]. Since, proline is a rigid amino acid, it may introduce structural constraints in protein folding, potentially affecting *COMT* enzyme function and dopamine breakdown.

This disruption in dopamine homeostasis could contribute to motor dysfunction and stereotyped behaviors, and hallmark features of catatonic SCZ [25-26]. One of the major challenges in psychiatric genetics is understanding the variability of genetic risk factors across populations. Most SCZ genome-wide association studies (GWAS) have been conducted in Japanese, European and East Asian populations [27-28]. Often neglecting genetic variants that may be unique to underrepresented populations. South Indian populations, including those from Tumkur district, have distinct genetic backgrounds, which may harbor rare or population-specific SCZ susceptibility alleles. Val158Met (rs4680), a widely studied *COMT* variant, shows varying allele frequencies across different ethnic groups, suggesting that regional genetic diversity may influence disease risk and symptoms [29].

The identification of novel *COMT* variants in this study reinforces the need for population-specific genetic research to enhance our understanding. From a clinical perspective, the identification of c.449A>T (p. Gln150Leu) and c.114G>C (p. Ala123Pro) mutations could have important implications for personalized medicine. Variants affecting dopamine metabolism may influence a patient’s response to antipsychotic medication, particularly dopamine D2 receptor antagonists, which are commonly used in SCZ treatment [30]. Prescribed, candidate gene like, COMT, FUT2 and MTHFR put down excruciate effect on quality of life and perimenopausal sympathetic health issues in women [31]. Understanding how *COMT* mutations affect dopamine regulation could aid in tailoring pharmacological treatments to individual patients based on their genetic profile, thereby improving treatment efficacy and reducing adverse effects.

Overall, this study identified two novel missense mutations in the *COMT* gene, contributing to our understanding of dopaminergic dysfunction in SCZ. These findings suggest that distinct *COMT* mutations may be associated with specific SCZ subtypes, further supporting the role of dopamine dysregulation in the disorder's pathophysiology. Given the genetic heterogeneity of SCZ, further large-scale population studies and functional analyses are warranted to validate these findings and explore their potential clinical applications in psychiatric genetics and personalized medicine. Novel variants their implication, to understand future female compliance like cancer, endocrine, metabolic syndrome clinical diagnostic and therapeutic applications. Exon: 4 no significance in healthy group in tumkur populations.

CONCLUSION: This study identified two novel missense mutations in exon 4 of the COMT gene, c.449A>T (p. Gln150Leu) and c.114G>C (p. Ala123Pro), in SCZ patients from Tumkur district, South Karnataka. These variants were classified as pathogenic based on *in-silico* prediction models and were found to correlate with distinct SCZ subtypes, with c.449A>T associated with paranoid SCZ symptoms and c.114G>C linked to catatonic SCZ symptoms. Other than, that novel mutation also adverse effect on female reproductive cycle would impact on other life issues. The COMT is a crucial enzyme in dopamine metabolism, mutations affecting its function may alter dopamine availability in the prefrontal cortex, potentially leading to cognitive and behavioral abnormalities observed in SCZ patients. The genetic architecture of SCZ is highly heterogeneous, and variants that are significant in one population may not necessarily be prevalent or functionally relevant in another. Studying underrepresented populations, such as those from South Karnataka, enables a more comprehensive understanding of genetic diversity in SCZ and may aid in the development of ethnically tailored diagnostic markers and treatment approaches. These findings suggest that distinct genotypic variations may contribute to different clinical phenotypes. Despite these significant findings, further research is essential to validate the functional consequences of these variants. *In-vitro* enzymatic studies, molecular docking simulations, and dopaminergic pathway analysis could provide deeper insights into how these mutations alter COMT function and contribute to dopamine imbalances in SCZ.

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CONFLICTS OF INTEREST: There are no conflicts of interest.

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