IJPSR (2026), Volume 17, Issue 7 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 February 2026; received in revised form, 24 March 2026; accepted, 23 April 2026; published 01 July 2026

NEUROPHARMACOLOGICAL IMPLICATIONS OF COMT GENE VARIANTS ON DOPAMINERGIC FUNCTION IN THE INDIAN POPULATION

K. G. Satheesh Kumar [1] and Soundarahari Saravanan [* 2]

Department of Pharmacology [1], Department of Physiology [2], SVMC, Tirupati - 517507, Andhra Pradesh, India.

Keywords:

Catechol-O-methyltransferase, COMT, COMT polymorphism, rs4680 (Val158Met), Dopamine metabolism, Pharmacogenomics

Correspondence to Author:
Soundarahari Saravanan

Final Year Postgraduate,
(M.D. Physiology)
Department of Physiology,
SVMC, Tirupati - 517507,
Andhra Pradesh, India.

E-mail: soundarahari@gmail.com

ABSTRACT: Background: Catechol-O-methyltransferase (COMT) is a key enzyme involved in dopamine metabolism in the brain. Genetic variation in the COMT gene, particularly the rs4680 (Val158Met) polymorphism, alters enzyme activity and influences dopamine availability in the prefrontal cortex. These differences can affect cognition, emotional regulation, stress response, and sensitivity to neuropsychiatric medications. Given India's high genetic diversity, population-specific evaluation of COMT variants is essential for personalized neuropharmacology. **Objectives:** To examine the functional and neurophysiological impact of common COMT gene polymorphisms in the Indian population using bioinformatic and simulation-based approaches. **Methods:** An *in-silico* descriptive study was conducted using allele frequency data from the IndiGenomes database. Five functionally relevant COMT variants (rs4680, rs4633, rs6269, rs4818, and rs737865) were analyzed. Functional effects were assessed using established computational prediction tools. Genotype frequencies were simulated in a hypothetical Indian cohort of 1,000 individuals based on Hardy–Weinberg equilibrium to infer dopamine tone and predicted drug response patterns. **Results:** The analysis demonstrated marked interindividual variability in COMT activity and predicted dopamine levels. Variants associated with reduced COMT function were linked to higher prefrontal dopamine availability, while regulatory variants influenced enzyme expression and dopamine turnover. These genetic differences translated into distinct predicted responses to stimulants, antidepressants, and antipsychotics. **Conclusion:** COMT polymorphisms significantly influence dopaminergic balance and neuropharmacological response in the Indian population. These findings support the potential utility of COMT genotyping in guiding personalized treatment strategies in psychiatry and neurology.

INTRODUCTION: Catechol-O-methyltransferase (COMT) is an important enzyme that helps regulate dopaminergic neurotransmission by breaking down catecholamines such as dopamine, epinephrine, and norepinephrine. By controlling how quickly these chemicals are cleared from synapses, COMT plays a key role in dopamine metabolism, which has downstream effects on brain functions related to emotion, cognition, and behavior. Genetic differences, especially in the well-known Val158Met (rs4680) variant of the COMT gene, can change the efficiency of the enzyme, which in turn affects dopamine availability in areas like the prefrontal cortex an essential region for memory, attention, and emotional control [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.17(7).2159-69

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.17(7).2159-69

Recent studies show that this rs4680 polymorphism doesn't just alter dopamine levels it can also affect how the body responds to stress, medication, and neurological stimuli. Differences in COMT activity due to the Val/Met substitution have been linked to variations in drug response, emotional regulation, and vulnerability to disorders such as anxiety, schizophrenia, and Parkinson's disease [2].

A recent 2023 meta-analysis confirmed that COMT rs4680 is significantly associated with levodopa-induced dyskinesia in patients with Parkinson's disease, particularly in Asian populations [2]. This highlights how even a single genetic change can influence the effectiveness and side effects of dopaminergic drugs. Similarly, a study on Indian children with ADHD found that COMT and other dopaminergic gene variants can affect impulsivity, attention, and cognitive function, showing that these genetic patterns have real behavioral consequences in Indian groups [3].

Pharmacogenetic studies in clinical populations suggest that COMT rs4680 variation can influence individual differences in drug response and adverse effects [4]. Such genetic variability can influence how individuals metabolize dopamine and respond to psychiatric medications.

Further, Recent reviews have highlighted the importance of considering ethnic variability in COMT-related pharmacological studies, particularly in Parkinson's disease, suggesting that dopamine metabolism involves complex gene–gene interactions [5]. Beyond movement disorders, COMT polymorphisms have also been linked to dopaminergic dysregulation and behavioral vulnerability, such as in opioid use disorder among Asian populations, showing that COMT's influence extends from molecular regulation to real-world psychological outcomes [6].

Taken together, these findings emphasize that COMT polymorphisms are not just genetic markers they are active players in shaping dopaminergic balance, emotional stability, and treatment response. By combining bioinformatic tools, population data, and neuropharmacological insights, this study aims to predict how common COMT variants in the Indian population influence dopamine metabolism and, consequently, neurobehavioral and pharmacological outcomes.

METHODOLOGY:

Data Sources: Publicly available genomic datasets were used for this *in-silico* analysis. Allele frequency data for COMT gene variants were obtained from the IndiGenomes database (CSIR-IGIB, India). Specifically, data were retrieved from the IndiGenomes Phase I release, comprising whole-genome sequencing data from 1,029 Indian individuals representing diverse ethnic and geographic groups across India.

Comparative global allele frequency data were obtained from the 1000 Genomes Project Phase 3 dataset, which includes genomic data from 2,504 individuals across 26 populations worldwide. Population groups were defined according to standard 1000 Genomes classification as East Asian (EAS), South Asian (SAS), and European (EUR).

Variant annotation and validation were performed using Database of Single Nucleotide Polymorphisms (dbSNP) Linkage disequilibrium (LD) (build 155) and the Ensembl Genome Browser (release 111), mapped to the GRCh38/hg38 human reference genome.

Allele frequency data were accessed on 15 December 2025. As database content and allele frequencies may be updated over time due to reanalysis and quality control filtering, the present study reflects the dataset version available at the time of retrieval.

The study focused on simulated genotype distributions (n = 1000) derived from these allele frequencies. As only secondary databases and computational tools were used, no ethical approval was required.

Allele Frequency Definition: Allele frequencies reported in this study represent alternate allele frequencies (AAF) as provided by the source databases. For each variant (rsID), the frequency corresponds to the second allele listed (alternate allele) in the "Alleles" column of **Table 2.** Minor allele frequency (MAF) was not separately calculated, as the alternate allele may not always represent the minor allele across populations.

Variant Selection: COMT variants were included if allele frequency data were available in the IndiGenomes database. Functionally relevant missense, synonymous, regulatory, and untranslated region (UTR) variants previously associated with dopaminergic metabolism or neuropsychiatric outcomes were prioritized.

The final panel included:

- rs4680 (Val158Met; missense variant)
- rs4818 (Leu136Leu; synonymous)
- rs4633 (His62His; synonymous)
- rs6269 (promoter/regulatory region variant)
- rs737865(Regulatory / intronic)

Functional Prediction Tools: SIFT (Sorting Intolerant from Tolerant) (v6.2.1).

Database: UniProt + RefSeq protein sequences Output: SIFT score (0–1) Threshold: ≤ 0.05 = deleterious; > 0.05 = tolerated.

PolyPhen-2 (v2.2.3) Polymorphism Phenotyping Models used: HumDiv and HumVar Output categories: Probably damaging (score > 0.85), possibly damaging (0.15–0.85), Benign (< 0.15).

PROVEAN (v1.1.5) Database: NCBI NR protein database with BLAST-based clustering Threshold: ≤ –2.5 = deleterious; > –2.5 = neutral CADD (v1.6).

Model: Combined Annotation–Dependent Depletion (GRCh38) Output: PHRED-scaled deleteriousness score Threshold: ≥ 15 = potentially damaging. I-Mutant 3.0 (Webserver 2023) Database: Protein Data Bank (PDB) reference structures Output: ΔΔG (kcal/mol); Threshold: < –0.5 = destabilizing MutationTaster 2 (2024 update) Database: Ensembl Variant Database + RefSeq annotation Output: Qualitative prediction ("disease causing" or "polymorphism").

Annotation of Non-Coding Variants: For synonymous and regulatory variants, protein-impact prediction tools are not directly applicable. Therefore, functional interpretation was based on published evidence regarding effects on mRNA stability, gene expression, and linkage disequilibrium with functional variants. Dedicated splicing or regulatory prediction tools were not systematically applied, which is acknowledged as a limitation.

Functional Interpretation Criteria: Functional interpretation of COMT variants was based on an integrative approach combining bioinformatic predictions and existing biological evidence. For coding variants, *in-silico* tools such as SIFT, PolyPhen-2, PROVEAN, and CADD were considered where applicable.

However, for synonymous and regulatory variants, which do not directly alter protein structure, functional significance was inferred based on known effects on gene expression, mRNA stability, and linkage disequilibrium with functionally established variants (e.g., rs4680).

The rs4680 (Val158Met) variant was considered functionally significant based on well-established experimental evidence demonstrating its effect on COMT enzyme activity, despite being predicted as tolerated or benign by protein-based computational tools. For rs4680, functional relevance was determined based on established biochemical evidence, including reduced enzyme stability and activity associated with the Met allele, rather than relying solely on protein-impact prediction tools.

Pharmacogenomic interpretations were derived from previously published studies on COMT function and dopaminergic drug response, and are presented as literature-based trends rather than primary findings of this study.

Population Analysis: Allele frequency data for each COMT variant were extracted from IndiGenomes. Expected genotype frequencies were calculated using Hardy–Weinberg Equilibrium (HWE) proportions (p^2, $2pq$, q^2), assuming a hypothetical population size of n = 1000 for proportional representation.

This simulation-based descriptive approach standardized genotype comparisons across loci and allowed visualization of the distribution of deleterious vs. tolerated variants within the Indian population.

Genotype counts were classified as follows:

- AA = reference homozygote
- Aa = heterozygote
- aa = alternate homozygote

The resulting distributions were used to describe the dopaminergic metabolism variation spectrum among Indian individuals. No statistical significance testing beyond HWE conformity was performed. Genotype frequencies were simulated under the assumption of Hardy–Weinberg equilibrium, acknowledging that this assumption may not fully capture the effects of population stratification within the Indian population.

Interpretation of Variant Effects: Metabolizer classification (fast, intermediate, poor) was applied only to the rs4680 (Val158Met) variant due to its well-established functional effect on COMT enzyme activity. Other variants (rs4633, rs6269, rs4818, rs737865) were interpreted based on their regulatory or haplotype-linked effects, as these variants do not independently determine enzyme activity.

Haplotype Consideration: Although several COMT variants analyzed in this study are known to form functional haplotypes (e.g., rs6269, rs4633, rs4818, rs4680, rs737865), haplotype frequencies were not computed due to the absence of individual-level genotype data. Therefore, variants were analyzed independently, and functional interpretations were limited to known regulatory or linkage-based effects. This study is descriptive in nature and based on computational analysis of allele frequencies and simulated genotype distributions. No inferential statistical comparisons were performed, and results are presented as observed trends rather than statistically validated differences.

Data Processing: All computations and tabulations were performed in Microsoft Excel (Microsoft Office 2021). Functional predictions were manually integrated with population-frequency data to infer variant-level contributions to COMT variability.

RESULTS:

TABLE 1: KEY COMT VARIANTS AND THEIR PREDICTED IMPACT ON DOPAMINERGIC NEUROTRANSMISSION

Variant (rsID)	Genomic Region	Variant Type	Effect on COMT Activity	Predicted Dopamine Tone
rs4680 (Val158Met)	Exon 4	Missense (G→A); Val → Met	Reflects reduced COMT activity	Relatively higher dopamine levels
rs4633	Exon 3	Synonymous (C→T; His62His)	Linked to reduced COMT activity, likely mediated through mRNA stability and linkage disequilibrium with rs4680	Relatively higher dopamine levels
rs6269	Intron 1 (5′ regulatory region)	Regulatory SNP (A→G)	Associated with increased COMT expression at the transcriptional level	Relatively lower dopamine levels
rs4818	Exon 4	Synonymous (C→G; Leu136Leu)	Thought to influence COMT activity through effects on mRNA secondary structure	Relatively lower dopamine levels
rs737865	Intron 1	Intronic / regulatory	Influences COMT expression indirectly through haplotype-linked regulatory effects	Variable (haplotype-dependent; inferred dopamine tone)

Table 1 shows how different COMT gene variants influence dopamine levels in the brain. Variants like rs4680 and rs4633 are linked to lower COMT activity, meaning dopamine tends to stay active longer in the prefrontal cortex. In contrast, rs6269 and rs4818 increase COMT function, leading to reduced dopamine levels, while rs737865 appears to fine-tune these effects depending on its genetic combination with other variants. Descriptions of dopamine levels are conceptual and represent relative inferences based on predicted COMT activity rather than directly measured concentrations.

TABLE 2: ALLELE FREQUENCY COMPARISON OF COMT VARIANTS: INDIAN POPULATION VS GLOBAL POPULATION FREQUENCIES (EAS, SAS, EUR) DERIVED FROM 1000 GENOMES PROJECT PHASE 3 DATASET

rsID	Alleles (Ref / Alt)	India	EAS	SAS	EUR
rs4680	G / A	0.4273	0.2798	0.4407	0.5000

rs4633	C / T	0.4370	0.2698	0.4448	0.4990
rs6269	A / G	0.3137	0.3423	0.3252	0.4125
rs4818	C / G	0.2924	0.3413	0.3149	0.4026
rs737865	A / G	0.2378	0.2937	0.2669	0.2813

Table 2 shows that COMT gene variants in the Indian population occur at frequencies that differ modestly from other global populations. Variants such as rs4680 and rs4633 are moderately common in Indians, with frequencies falling between those observed in East Asian and European populations. However, these differences should be interpreted cautiously, as the comparisons are based on data derived from different datasets with varying sample compositions, quality control filters, and population definitions. Therefore, the observed variations may reflect underlying sampling differences rather than true biological divergence.

TABLE 3: COMPUTATIONAL *(IN-SILICO)* ANNOTATIONS OF COMT VARIANTS

Variant (rsID)	Variant Class	Protein-level Change	SIFT	PolyPhen-2	Mutation Taster	Interpretation
rs4680 (Val158 Met)	Missense	Val → Met at codon 158	(0.23) Tolerated	(0.01) Benign	Polymorphism	Predicted as tolerated/benign by protein-impact tools; however, extensive biochemical evidence Suggests that the Val158Met substitution reduces COMT enzyme thermal stability and activity, resulting in decreased dopamine degradation.
rs4633	Synonymous	None	Not applicable	Not applicable	Not applicable	Synonymous variant; associated with altered mRNA stability and translation efficiency, and acts in linkage disequilibrium with functional variants such as rs4680.
rs6269	Intronic (regulatory)	None	Not applicable	Not applicable	Not applicable	Intronic regulatory variant; associated with altered transcriptional activity and COMT gene expression (regulatory effect), without direct impact on protein structure.
rs4818	Synonymous	None	Not applicable	Not applicable	Not applicable	Synonymous variant; alters mRNA secondary structure and translation efficiency, indirectly modulating COMT activity.
rs737865	Intronic (regulatory)	None	Not applicable	Not applicable	Not applicable	Intronic regulatory variant; functionally relevant through linkage disequilibrium with COMT haplotypes, contributing to variation in gene expression.

Table 3 shows the functional importance of COMT gene variants identified in the Indian population based on computational predictions. The rs4680 (Val158Met) variant, though predicted as benign by most tools, is functionally significant because it reduces COMT enzyme stability and activity, leading to higher dopamine levels in the brain. The rs4633 and rs4818 variants, while synonymous, are linked to changes in mRNA folding and translation efficiency, indirectly affecting enzyme production.

Similarly, rs6269 and rs737865, located in regulatory regions, may control COMT gene expression, influencing how much enzyme is formed. Overall, these variants especially rs4680 and its linked partners form a functionally meaningful haplotype that can alter dopaminergic tone and neurophysiological responses in the Indian population.

TABLE 4: COMT POLYMORPHISMS: FUNCTIONAL INTERPRETATION IN A SIMULATED INDIAN POPULATION (N = 1000)

Variant (rsID)	Genotype	Functional Interpretation	Expected Count (n/1000)	Dopamine Levels	Interpretation
rs4680 (Val158 Met)	GG (Val/Val)	Fast metabolizer	327	Low	Higher COMT activity is linked to relatively lower dopamine levels and is suggestive of differences in executive function and stress response.
	GA (Val/Met)	Intermediate metabolizer	490	Moderate–High	Partial reduction in COMT activity reflects a balanced dopamine tone and is indicative of intermediate cognitive performance and stress sensitivity.
	AA (Met/Met)	Poor metabolizer	183	High	Reduced COMT activity is linked to relatively higher dopamine levels and is suggestive of enhanced working memory alongside increased susceptibility to stress and anxiety.
rs4633	CC	Associated with relatively higher COMT activity (haplotype-linked)	317	Low–Moderate	Reflects relatively lower cortical dopamine availability through haplotype-linked effects.
	CT	Intermediate haplotype-linked effect	492	Moderate	Indicates intermediate dopamine tone with potential variability in cognitive and behavioral traits.
	TT	Associated with reduced COMT activity (haplotype-linked)	191	Moderately high	Linked to relatively higher dopamine levels through association with functional variants such as rs4680.
rs6269	AA	Associated with higher COMT expression (regulatory effect)	471	High	Increased COMT expression is linked to lower dopamine levels and is suggestive of differences in attention and cognitive flexibility.
	AG	Intermediate regulatory effect	431	Moderate	Reflects balanced COMT expression and dopamine metabolism.
	GG	Associated with reduced COMT expression (regulatory effect)	98	Low	Reduced COMT expression is linked to relatively higher dopamine levels and may influence cognitive and emotional processing.
rs4818	CC	Associated with higher COMT activity (mRNA structural effect)	500	High	Reflects increased COMT activity and relatively lower dopamine levels.
	CG	Intermediate effect	414	Moderate	Indicates intermediate dopaminergic signaling.
	GG	Associated with reduced COMT activity	86	Low	Linked to relatively higher dopamine levels due to reduced COMT activity.
rs737865	AA	Associated with higher COMT expression (haplotype-linked)	580	High	Influences COMT expression through haplotype-linked effects, contributing to lower dopamine availability.

	AG	Intermediate haplotype-dependent effect	363	Variable	Reflects variability in dopamine levels depending on linkage with other functional variants.
	GG	Associated with reduced COMT expression (haplotype-linked)	57	Low	Linked to relatively higher dopamine levels through haplotype-associated regulatory effects.

Table 4 presents the predicted functional impact of COMT variants in a simulated Indian population of 1,000 individuals. The results highlight substantial genetic variability influencing dopaminergic regulation. The rs4680 (Val158Met) variant Suggests a clear functional gradient, with intermediate (GA) and poor (AA) metabolizer genotypes associated with relatively higher dopamine availability compared to the fast metabolizer (GG) genotype.

In contrast, other variants such as rs4633, rs6269, rs4818, and rs737865 do not independently define metabolizer status but contribute to COMT activity through regulatory mechanisms or linkage disequilibrium with functional variants. These SNPs exhibit modulatory effects on enzyme expression, mRNA stability, or haplotype-dependent activity, leading to variability in dopamine tone across individuals.

Overall, these findings suggest that while rs4680 serves as a primary functional determinant of COMT activity, other variants act as modifiers within a broader genetic framework, collectively contributing to interindividual differences in dopaminergic balance and neuropharmacological response. Behavioral and cognitive interpretations are derived from prior literature and are consistent with established associations in COMT-related dopaminergic regulation

TABLE 5: NEUROPHARMACOLOGICAL EFFECTS OF COMT POLYMORPHISM

Variant (rsID)	Genotype	Count	Stimulants	Antidepressants	Antipsychotics
rs4680 (Val158Met)	GG (Val/Val)	328	Suggests relatively lower baseline dopamine with comparatively reduced responsiveness to stimulants, as reported in prior studies.	Suggests comparatively lower response in cognitive domains.	Associated with a comparatively lower risk of extrapyramidal symptoms (EPS).
	GA (Val/Met)	490	Reflects intermediate response patterns.	Suggests moderate variability in response.	Reflects typical response patterns.
	AA (Met/Met)	183	Associated with increased sensitivity to stimulants and a higher likelihood of adverse effects such as anxiety or insomnia.	Suggests increased sensitivity and variability in response.	Associated with increased susceptibility to adverse effects such as EPS or cognitive blunting.
rs4633	CC	317	Suggests relatively reduced dopaminergic tone through haplotype-linked effects, potentially influencing treatment response.	Suggests variability in treatment response.	Reflects typical to comparatively reduced response patterns.
	CT	492	Reflects intermediate response patterns.	Suggests moderate variability in response.	Reflects typical response patterns.
	TT	191	Associated with relatively higher dopamine levels through haplotype effects, potentially increasing sensitivity.	Suggests increased sensitivity to treatment.	Associated with an increased likelihood of adverse effects.
rs6269	AA	471	Suggests increased COMT expression with relatively lower dopamine levels,	Suggests variability in treatment response.	Reflects relatively reduced dopaminergic tone.

			potentially contributing to reduced responsiveness.		
	AG	430–431	Reflects intermediate response patterns.	Suggests moderate variability.	Reflects typical response patterns.
	GG	98	Associated with relatively higher dopamine levels due to reduced COMT expression, potentially increasing sensitivity.	Suggests variability in response.	Associated with increased susceptibility to adverse effects.
rs4818	CC	501	Suggests altered COMT activity with relatively reduced dopamine tone.	Suggests variability in treatment response.	Associated with variability in adverse effect profile.
	CG	414	Reflects intermediate response patterns.	Suggests moderate variability.	Reflects typical response patterns.
	GG	86	Associated with relatively higher dopamine levels due to reduced COMT activity.	Suggests increased sensitivity to treatment.	Associated with increased susceptibility to adverse effects.
rs737865	AA	581	Suggests haplotype-linked influence on COMT expression, potentially affecting treatment response.	Suggests variability in response.	Associated with variability in adverse effect profile.
	AG	363	Reflects variable response patterns depending on haplotype context.	Suggests variable response.	Reflects variable response patterns.
	GG	57	Associated with altered COMT expression and dopamine levels through haplotype-associated effects.	Suggests variability in response.	Associated with differences in adverse effect susceptibility.

Table 5 shows how different COMT gene variants can influence an individual's response to common neuropsychiatric medications in the Indian population. People with the poor metabolizer genotypes (like AA for rs4680 or TT for rs4633) tend to have higher dopamine levels, which makes them more sensitive to stimulants and antipsychotics, often requiring lower doses to avoid side effects such as anxiety or extrapyramidal symptoms (EPS). In contrast, fast metabolizers (such as GG for rs4680, GG for rs4818, and GG for rs737865) break down dopamine faster and usually need higher medication doses to achieve therapeutic effects. The intermediate genotypes show balanced dopamine levels and typically respond to standard doses across drug classes. Overall, these results indicate that COMT polymorphisms meaningfully affect drug response patterns, emphasizing the potential value of personalized dosing strategies in the Indian population based on COMT genotype. The pharmacological interpretations presented are based on previously reported pharmacogenomic studies and theoretical inference. These findings do not constitute clinical dosing recommendations and should not be used for treatment decisions.

DISCUSSION: This study explored how key COMT gene polymorphisms may influence dopamine metabolism and neurophysiological responses in the Indian population. Our findings suggest that genetic variability, particularly in rs4680 (Val158Met), may contribute to differences in dopamine turnover and may be associated with variation in stress reactivity, cognitive function, and mood regulation. Previous studies have reported similar associations, indicating that individuals with the Met allele may exhibit relatively higher baseline dopamine levels, and that COMT genetic variation may contribute to differences in stress adaptation and population-level resilience patterns [7]. Although *in-silico* tools classify rs4680 as tolerated, its functional relevance has been supported by biochemical studies demonstrating reduced COMT enzymatic activity and altered dopamine metabolism.

The interaction between COMT activity and stress response has been described as an important factor in neurophysiological regulation. Glavač *et al.* (2025) reported associations between COMT rs4680 variants and specific emotion-related traits, suggesting a potential role of dopaminergic genetic variation in affective phenotypes [8]. Similarly, Magwai and Xulu (2022) highlighted the role of genetic factors in modulating physiological responses to chronic stress and stress-related disorders [9]. These observations are broadly consistent with the trends observed in our simulation-based analysis, which suggest variability in inferred dopamine tone across different genotypes.

Beyond stress modulation, COMT variation may also be relevant to neurocognitive and psychiatric outcomes. Recent evidence suggests that COMT rs4680 interacts with broader dopaminergic mechanisms to influence cognitive function and psychiatric phenotypes, particularly in disorders such as schizophrenia [10]. In line with these findings, our results suggest that individuals carrying the Met/Met genotype may exhibit differences in dopamine-related neural activity, which could be associated with variation in working memory performance as well as emotional regulation. However, these interpretations should be considered exploratory given the simulation-based nature of the study. The medication-response patterns described are based on prior pharmacogenomic literature and should be interpreted as hypothesis-generating rather than clinically validated observations.

From a pharmacogenomic perspective, variability in COMT activity may contribute to differences in response to neuroactive medications. Recent pharmacogenomic and addiction-related studies suggest that COMT rs4680 may influence dopaminergic signaling in reward pathways, contributing to variability in behavioral responses and susceptibility to addictive processes [11].

Consistent with this, our findings suggest that individuals with lower COMT activity (e.g., rs4680 Met/Met genotype) may exhibit increased sensitivity to certain psychotropic agents, whereas those with higher COMT activity may show comparatively reduced sensitivity. These observations are consistent with the broader concept of personalized psychiatry; however, clinical validation is required before any therapeutic implications can be drawn. Finally, Tabolacci *et al.* (2025) highlighted the role of biogenic amine metabolism genes, including COMT, in neurodevelopmental and cognitive phenotypes [12]. Taken together, these findings suggest that COMT variants particularly rs4680, along with haplotype-linked variants such as rs4633, rs6269, rs4818, and rs737865 may collectively contribute to variability in dopaminergic regulation, cognition, stress adaptation, and pharmacological response. Future studies incorporating haplotype-based analysis may provide a more comprehensive understanding of the combined functional effects of COMT variants.

Strengths: A key strength of this study is its focus on an Indian genomic dataset (IndiGenomes), allowing for population-specific interpretation of COMT polymorphisms. The study integrated computational functional predictions with bioinformatic modeling, giving a detailed view of how each variant may affect dopamine regulation. Moreover, the Hardy–Weinberg-based simulation provided a reliable representation of genetic distribution in a 1,000-individual Indian cohort, offering insights into real-world variability. Unlike earlier global studies, this analysis contextualizes COMT genetic effects within India’s unique genetic diversity, making it relevant for the development of region-specific pharmacogenomic guidelines.

Limitations: This was a computational and descriptive study without experimental or clinical validation. The predictions rely on *in-silico* tools, which, while powerful, cannot capture dynamic neurobiological processes or gene–environment interactions. Moreover, dopamine regulation involves several other genes (*e.g.*, DRD2, MAOA, and SLC6A3) that were not included here.

The sample simulation (n=1000) assumes Hardy–Weinberg equilibrium and may not account for subpopulation stratification within India. The assumption of Hardy–Weinberg equilibrium may not fully hold in the Indian population due to population stratification, genetic substructure, and endogamy, which can influence allele and genotype distributions. Finally, the absence of clinical phenotype data limits correlation with stress-related or neuropsychiatric outcomes. Haplotype-level analysis of COMT variants was not performed. Given that several COMT polymorphisms act in linkage disequilibrium, the absence of haplotype frequency estimation may limit the interpretation of combined genetic effects Dedicated splicing or regulatory prediction tools (e.g., SpliceAI, RegulomeDB, GTEx eQTL data) were not systematically applied due to the descriptive design of this study and lack of variant-level functional annotation integration Dopaminergic function and drug response are influenced by multiple genetic and non-genetic factors. In addition to COMT, other genes involved in dopamine signaling pathways (e.g., DRD2, MAOA, SLC6A3) may contribute to variability in neurophysiological and pharmacological responses. Furthermore, environmental influences, comorbid conditions, and concurrent medications can significantly affect treatment outcomes. Therefore, COMT genotyping alone is insufficient to guide clinical decision-making, and findings from this study should be interpreted within a broader, multifactorial context. Comparisons between Indian and global populations are based on data from different genomic datasets, which may vary in sampling strategies, quality control procedures, and ancestry definitions. These factors may introduce bias and limit direct comparability of allele frequencies.

CONCLUSION: This study Suggests that COMT polymorphisms, particularly rs4680 (Val158Met) and its linked variants, have meaningful effects on dopamine metabolism, stress regulation, and neurophysiological functioning in the Indian population. These genetic variations contribute to differences in emotional resilience, cognitive control, and drug responsiveness. Recognizing such variability is essential for advancing personalized neuropharmacology, where treatment strategies can be tailored based on an individual's genetic makeup. Future studies integrating clinical, neuroendocrine, and imaging data are needed to validate these bioinformatic findings and strengthen their translation into precision psychiatry and neurology.

ACKNOWLEDGEMENTS: Nil

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Sridharan K, Jassim A, Qader AM and Pasha SAA: Unraveling the Role of COMT Polymorphism in Dopamine-Mediated Vasopressor Effects: An Observational Cross-Sectional Study. Curr Drug Metab 2024; 25(2): 152-156. doi: 10.2174/0113892002293952240315064943
2. Dwivedi A, Dwivedi N, Kumar A, Singh VK, Pathak A, Chaurasia RN, Mishra VN, Mohanty S and Joshi D: Association of Catechol-O-Methyltransferase Gene rs4680 Polymorphism and Levodopa Induced Dyskinesia in Parkinson's Disease: A Meta-Analysis and Systematic Review. J Geriatr Psychiatry Neurol 2023; 36(2): 98-106. doi: 10.1177/08919887221103580.
3. Maitra S, Chatterjee M, Roychowdhury A, Panda CK, Sinha S and Mukhopadhyay K: Specific dopaminergic genetic variants influence impulsivity, cognitive deficit, and disease severity of Indian ADHD probands. Mol Biol Rep 2022; 49(8): 7315-7325. doi: 10.1007/s11033-022-07521-y.
4. Khan A, Waheed A, Afsar T, Abusharha A, Shafique H and Razak S: Unraveling Catechol-O-Methyltransferase rs4680 SNP's Role in Patients' Response to Tramadol and Its Adverse Effects: A Pharmacogenetics Insight into Postoperative Pain Management. J Clin Med 2023; 13(1): 249. doi: 10.3390/jcm13010249.
5. Poplawska-Domaszewicz K, Limbachiya N, Qamar M, Batzu L, Jones S, Sauerbier A, Rota S, Lau YH and Chaudhuri KR: Addressing the Ethnicity Gap in Catechol O-Methyl Transferase Inhibitor Trials in Parkinson's Disease: A Review of Available Global Data. J Pers Med 2024; 14(9): 939. doi: 10.3390/jpm14090939.
6. Huang X, Wang C, Zheng L, Ren L, Jin T, Yu Z and Tang Y: Significant Association of the Catechol-O-Methyltransferase Gene Polymorphism (rs4680) and Opioid Use Disorder in Asian Populations, but not Caucasian Populations: A Meta-analysis. Genet Test Mol Biomarkers 2022; 26(6): 316-323.
7. Mikhailova SV, Ivanoshchuk DE, Yushkevich EA, Bairqdar A, Anisimenko MS, Shcherbakova LV, Denisova DV and Orlov PS: Prevalence of Common Alleles of Some Stress Resilience Genes among Adolescents Born in Different Periods Relative to the Socioeconomic Crisis of the 1990s in Russia. Curr Issues Mol Biol 2022; 45(1): 51-65. doi: 10.3390/cimb45010004.
8. Glavač T, Barbo M, Ravnik-Glavač M, Zupančič M and Dolžan V: Molecular genetic basis of the primary emotions in young adults: an exploratory analysis of genetic polymorphisms across dopamine, serotonin, oxytocin, endogenous opioid, and neurotrophic factor pathways. Front Pharmacol 2025; 16: 1675538. doi: 10.3389/fphar.2025.1675538.
9. Magwai T and Xulu KR: Physiological Genomics Plays a Crucial Role in Response to Stressful Life Events, the Development of Aggressive Behaviours, and Post-Traumatic Stress Disorder (PTSD). Genes (Basel) 2022; 13(2): 300. doi: 10.3390/genes13020300.
10. Maksimenko T, Zorkina Y, Efimova O, Andriushchenko A and Kostyuk G: Association of the COMT Gene Polymorphism rs4680 with Cognitive Impairment in Schizophrenia: A Narrative Review. Consort Psychiatr 2025; 6(3): 62-70. doi: 10.17816/CP15603.
11. Drevin G, Pena-Martin M, Bauduin A, Baudriller A, Briet M and Abbara C: Pharmacogenomics of 3,4-Methylenedioxymethamphetamine (MDMA): A Narrative Review of the Literature. Pharmaceutics 2024; 16(8): 1091. doi: 10.3390/pharmaceutics16081091.
12. Tabolacci C, Caruso A, Micai M, Galati G, Lintas C, Pisanu ME and Scattoni ML: Biogenic Amine Metabolism and Its Genetic Variations in Autism Spectrum Disorder: A Comprehensive Overview. Biomolecules 2025; 15(4): 539. doi: 10.3390/biom15040539.

How to cite this article:
Satheeshkumar KG and Soundarahari S: "Neuropharmacological implications of COMT gene variants on dopaminergic function in the Indian population". Int J Pharm Sci & Res 2026; 17(7): 2159-69. doi: 10.13040/IJPSR.0975-8232.17(7).2159-69.