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Role of Genotype Activities of COMT Gene in Male Schizophrenia Patients, Tumkur District, South Karnataka

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ABSTRACT

Introduction: Schizophrenia (SCZ) is a neuropsychiatric & multi-symptomatic disease. Catechol-O-Methyltransferase (COMT) gene is candidate gene associate with SCZ. COMT gene [Catecho-O-methyltrasnferase] encodes enzymatic activity, which interlink with various metabolic pathways like steroidal hormonal pathways.

COMT gene exits multiple polymorphic forms, genotype activity and their affects' associated with phenotypes & sex hormonal production.

Aim: The study was designed to evaluate the genotype activity associate with male SCZ patients in Tumkur district, South Karnataka.

Objectives:

- To study of COMT genotype in exon: 3 & exon: 4.
- To study of genotype activity on sex-hormonal biochemical serum marker.

Subjects & methods: The study was performed on 80 SCZ patients & 80 healthy groups between 16-70 years. We procured blood samples for DNA isolation. Thermo cycle reaction [PCR] was used to amplify the COMT gene, 1% Agarose gel electrophorisis, Sanger sequencing. For hormonal analysis was done by CLIA method.

Results: This study analyzed demographic information from male schizophrenia patients. The mutational genotypes G/A [Val/Met], C/T [H62H] & G/C [Ala/Ala] associated with symptoms. However, G/A [Val/Met] & C/T [H62H] are strongly associated with serum E2 & Testosterone level are found [$P<0.01$] statistically significant.

Conclusions: The genotype activity of the COMT gene distinguishes from genotype to genotype. In this study results concluded, that the genotype of COMT genes G/A [Val/Met] & C/T [H62H] are strongly associated with phenotypes and

serum E2 & Testosterone level in schizophrenia patients in Tumkur district. Moreover, we focus on molecular docking and epigenetic modification.

Keywords: *COMT gene, Genotypes, symptoms, sex-steroid hormones.*

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1. INTRODUCTION

Schizophrenia is worldwide a chronic and multi-complex, neuropsychiatric diseases which is associated with highly complex symptoms like cognitive and emotional and heterogenous symptoms [1]. As evidence, enzymes are potential substances, metabolic degradations like, of several neurochemicals, catecholamines, serotonin and nonadrenalin and linked with Catechol-O-methyltransferase (COMT) enzyme activity [2]. COMT enzyme help maintains accurate level of neurochemicals in the brain [3]. COMT enzyme encoded by COMT gene, is crucial for authenticate several neurotrsmitters pathways, like dopamine, epinephrine, and norepinephrine, hence, which reduce degrades neurotrsmitters pathways, physiological and psychological process such as stress, mood, and cognition[4]. SNP (single nucleotide polymorphism) of the COMT gene which associate with enzymatic activity methionine [Met=allies'] quarter of dopamine determining enzymatic activity Valine [Val = allies] [5]. As previous genetic investigations, clearly stated that COMT and MAO *[Mono amino oxidase]* deliberate effect on gene, sex interaction in various psychiatric diseases, even schizophrenia [6]. In addition, the COMT enzyme is more particularly associated on inactivate of catecholaminergic neurotransmitters pathways in prefrontal segment of brain cerebral cortex [7]. The enzyme *COMT* plays a cardinal role in moderating dopamine levels in the PFC, which is essential for executive function, cognitive flexibility, and working memory [8].

2. MATERIAL & METHODS:

2.1 Study samples:

The 80 individuals diagnosed with SCZ male patients and 80 healthy subjects ages between the 18 to 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 (SIMS&RH), Tumkur, Karnataka were included after taking the inform consent from the patients. This study was performed by using guideline of the Declaration of Helsinki and accepted by IEC [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 attendance 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. 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.

2.2 Inclusion & exclusions criteria:

The patients observed with schizophrenia in accordance with DSM-IV were included in the study. Patients diagnosed with psychiatric disorders other than schizophrenia were excluded from the study. In addition, control subjects excluded all neuropshicatric compliances, other health issues.

2.3 DNA isolation:

250µL of blood sample were used for acquisition of genomic DNA from the G. Bio Science Kit method, followed by manufacturer's protocol. The perfection and quantity of extracted DNA were assessed by using Namedrop spectrophotometry (USA: Thermo Fisher Scientific Inc.) by measuring at 260/280 nm absorbance ratio to confirm DNA purity. The reaction mixture was run on 1.5% gel electrophoresis with ethidium bromide (1µg/ml) and DNA was visualized under a UV transilluminator.

2.4 Polymorphism of COMT gene:

Amplication of COMT gene exon: 3 & exon: 4

Amplication of COMT gene primer design software using forexon:3 [senseprimer5'CAAGCAAAGGGGCGTGTG3', anti-sense is 3'TCCTGTAAGGGCTTTGATGC5'] and exon:4 [sense5'GTTCCCCTCTCTCCACCT3'anti-sense is 3'GTCTTTCCTCAGCCCCAG-5']. Total PCR amplification reaction mixture is 100ng of DNA template, 1.5µl of each primer, 1.5Mm $MgCl_2$, 2mM dNTPS and 10.8µl H_20.Master mixture is 15.5µl]. PCR reaction mixtures were obtained 35 cycles. The steps followed for the **exon: 3 [290bp]** was run denaturing for 1 minute at 94℃, 45s annealing at 62℃ at 1 minute, 1 minute's extensions at 72℃ for 5 minutes. **For exon:4 [190bp]** followed by Denaturing for 5 minutes at 95℃ followed by 35 times, 95℃ for 30 seconds, annealing at 62℃ for 1minute, extension at 72℃ for 45 seconds, cycle ends and final extension 72℃ for 7 minutes. The Amplication were visualized in 1.5% agarose gel stained using ethidium bromide and images were obtained using a gel documentation system.

2.5 Biochemical analysis

The superficial accessible [Median cubital] venous blood samples were collected than centrifuged at 3500rpm for 15 min.After extracting the serum sample, biochemical evaluation was carried out for the concentration of serum estrodiol [E2] and testosterone analyzed by Chemiluminescence Immunoassay (CLIA). For estimation of serum E2 and testosterone were purchased diagnostic kits from Erba.

2.6. Statistical analysis:

While, statistical analysis were done by using statistical software tool [SPSS computer software program] version 11.0 (Chicago, IL, USA) and Chi-square test For Qualitative data, differences among groups were tested by using Pearson's chi-square test (X2). P-value < 0.05 was considers significant. In healthy group statistical significance (P<0.001).

3. RESULTS:

Table: 1 To study of exon: 3 & exon:4 genotype with Phenotypes in male schizophrenia patients

Genotype	Positive symptoms	Negative symptoms	Cognitive	Symptoms	Total	%
C/T[H62H]	10	4	6	H=6, D=4, BE=6, A=2,Associality=1 Avolition=1.	20	31.8%
G/A[Val/Met]	18	8	1	H=4,De=5, Be=10, Anhid=4, Alogia=4.	27	42.8%
C/G[L/L]	11	4	1	H=2, DE=3, BE=6, Alogia=2, Anhidia=2, Associative=1	16	25.4%

*****H=hallucination, D=Delusion, B=Behaviour, A=Alogia, A=Associality, A=Avolition.

In Table.1 shows identification of Exon: 3 & exon: 4 genotypes in schizophrenia patients, however, each genotype potential associated with positive, negative, cognitive symptoms. In overall symptoms, genotype C/T [H62H] associated with symptoms [31.8%] symptoms, in genotype, G/A [Val/Met] associated with [42%] & in genotype C/G [L/L] associated with [25.4%]. So that, all the genotype associated with SCZ phenotype symptoms, more over H62H & Val108 Met strongly associated with phenotypes.

Table: 2 To study of exon:3 & exon:4 genotype among serum Estrodiole (E2) in schizophrenia male patients.

Genotype	**Mean ± SD**	**Kruskal-wallis**	**P-value**
C / T (n=51)	14.22 ± 6.70	31.072	1.7899 e-7
G / A (n=19)	29.09± 10.66		
C / G (n=27)	22.51± 15.34		

*P-value :< 0.001.

Table: 3. To study associate genotypes among serum Estrodiole (E2) in schizophrenia patients.

Genotype		W	P-value
G/A	C / T	7.41	<0.001
G/A	C/ G	2.65	0.145
C/T	C/ G	487	0.002
W is Dwass-Steel-Critchlow-Fligner (DSCF) test statistic			

Table 2 results shows that the serum Estrodiole (E2) mean± SD levels in COMT gene, genotypes pair C/T is 14.22 ± 6.70, in genotype G /A is 29.09± 10.66 and in genotype C / G is 22.51± 15.34. **Table.3** shows G/A& C/T genotype significantly found with serum E2 (P<0.01).However genotype of G/A & C/G (P<0.145) and C/T & C/G (P<0.002) are not found statistically. COMT gene, genotypes pair G/A & C/T strongly associated with serum Estrodiole (E2) level. So that, COMT gene enzymatic may be similar.

Table: 4.To study of exon: 3 & exon: 4 genotype with serum testosterone in schizophrenia male patients.

Genotype	MEAN ± SD	Kruskal-wallis test	P-value
C / T (n=51)	222.35± 12.83	17.458	<0.0001
G / A (n=19)	373.37± 10.65		
C / G (n=27)	251.49 ± 14.11		

Table: 5. To study of exon: 3& exon: 4 genotype associate with serum testosterone in schizophrenia patients.

Genotype		W	P-value
G /A	C / T	5.090	0.001
G /A	C / G	0.473	0.940
C /T	C / G	4.471	0.004
W is Dwass-Steel-Critchlow-Fligner (DSCF) test statistic			

Table 4 results shows that the serum testosterone mean± SD levels in COMT gene, genotypes pair C/T is 222.35± 12.83, in genotype G /A is 373.37± 10.56and in genotype C / G is 251.49 ± 14.11.**Table. 5** shows G/A& C/T genotype significantly found with serum testosterone (P<0.001).However genotype of G/A & C/G (P<0.145) and C/T & C/G (P<0.002) are not found statistically significance. Genotypes pair G/A & C/T of COMT gene are strongly integrated with serum Estrodiole (E2) level. So, those COMT genotypes and their enzymatic activity distinguish from genotype to genotype.

4. DISCUSSIONS:

Autosomal co-dominates alleles of COMT gene, polymorphism to associate with different enzymatic activity [9]. Neither genetic variants nor the catalytic activity of the enzymes have great intrinsic influence on schizophrenia risk [10]. Genotypes of Val/Val, Met/Met, and Val/Met of COMT gene effect on enzymatic activity [11]. COMT gene polymorphism Val/ met [G/A] is associated with decreases COMT enzyme activity [12]. Variants of COMT gene rs4680 & rs4633 both are polymorphism of COMT gene [SNP] would alter enzymatic activity, strength of neurotransmitters and hormonal circulations [13]. Moreover, rs4680 COMT genetic variant associated with Val/Met and Val/Val genotype effectively link with enhance higher enzymatic activity & reduce dopamine level than met/met genotype. Consequently, heterozygous genotype [Val/Met] shows more stable enzyme activity and reduce neuro-chemicals like Dopamine[14]. Distinguishing genotype of COMT gene allied with various enzymatic activities, which potentially impact on path physiology, neuropsychology, and clinical psychiatric abnormalities [15]. SNP of the COMT gene can be change on protein product at 158 Val/Met. The Met allies homozygosis condition reduced four times more enzyme activities of the COMT gene and is responsible for the inactivation of neurochemicals in the prefrontal cerebral cortical region, as well as emotional regulation & executive function [16-18]. SNP associated with various integrated pathways, like thyroid homeostasis, gut microbial

and hormonal [19]. Moreover, COMT Genotype activity is integrated with deteorition of stress performs regulation, nutrition metabolism, and rise catechol like dopamine, nor-epinephrine and epinephrine [20]. Val/Val of COMT gene significantly associated with serum estrogen imbalance in women's [21]. The COMT gene exhibits various genotype alleles; However, Valine confers stronger COMT activity than Methionine affecting dopamine concentration in the prefrontal cortex [22-24].There have been only a few research work on the evidence –based interlink of genotypes with hormonal fluctuations. The effect of genotype on hormonal level is not significance so far; however, genotypes can change or else be associated with hormonal imbalance [25]. However, In between male and female gender diversity might also reflect the ability of testosterone and dihydrotestosterone (DHT)[26]. Genome wide association study (GWAS) has been to detect genomic position are interlink with group of traits in populations [27]. The study of COMT genotype analysis reveals that a more active genotype is associated with sex hormones in SCZ. The present research study shows that genotype activity in SCZ patients in Tumkur district differs from genotype to genotype depending on genders. The genotype C/T [H62H] homozygous in exon: 3, while, genotype of the COMT gene in exon: 4 is G/A [Val/Met] and G/C [L/L] homozygous genotype were noted. It was confirmed that the genotype of the G/A [Val/Met] and C/T [H62H] pair is more strongly associated with phenotypes and sex-hormonal in male SCZ patients.

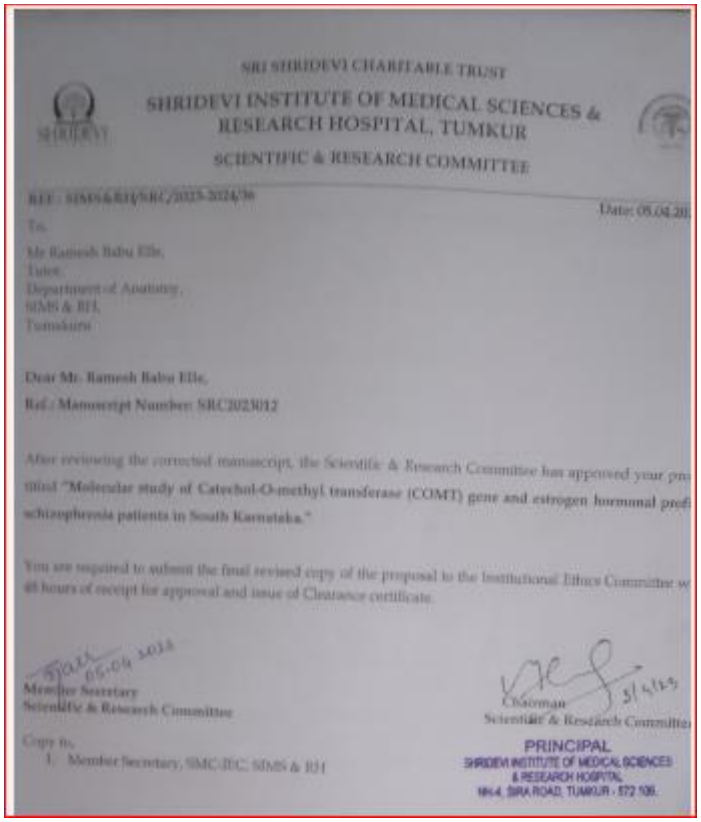
5. CONCLUSIONS:

The COMT gene is a potential candidate gene for SCZ. The mutations found in exon: 3 & exon: 4 of COMT gene shows distinguish enzymatic activity from genotypes to genotypes. The COMT gene of the H62H and Val/Met genotypes are strongly bound with Estrodiole [E2], Testosterone and other phenotypes in male SCZ patients. According to this study, H62H and Val/Met genotypes are significantly active genotypes and their enzymatic activity has a greater effect on male sex hormones in SCZ patients in Tumkur district. However, the enzymatic activity of the COMT genotype is might be influenced by molecular epigenetic changes. Future studies need to focus more on the correlation between genotype activity in phenotype symptoms in male and female patients, also focus on molecular docking and epigenetic modification.

Conflict of interest:
This is my so I finally declared was no conflict of interest. In this work no one financial and personal relationship with organizations.

Declarations:

- **Ethical approval.**



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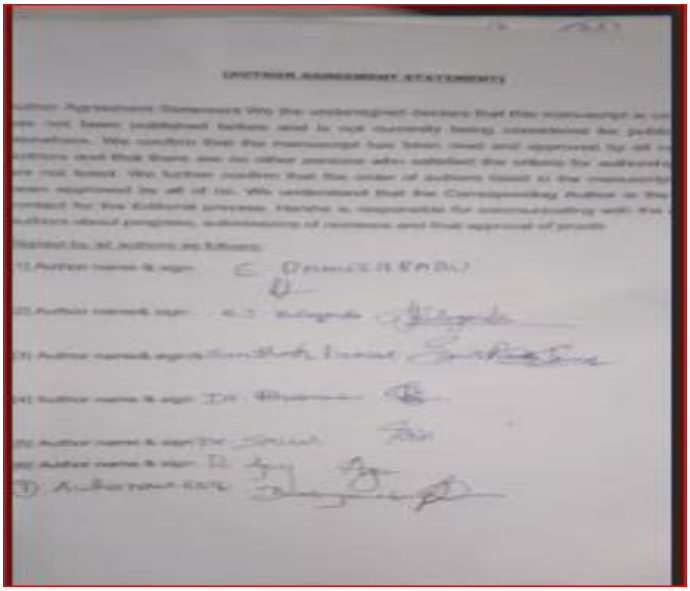

- **Availability of data and material:**

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Primary data: My original research work.
I collected Schizophrenia patients.

- **Competing interest:**

All listed authors must declare any competing interests relevant to, or which can be perceived to be relevant to the article. A competing interest can occur where the authors (or their employer, sponsor or family/friends) has legal or professional relationship with other organizations, or with the people working with them which could influence the research or interpretation of the results.

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Author's contributions:

Author agreement statement we the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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