Review Article

Genetic Insights into Cannabis-induced Psychosis: Role of CNR1 Gene Mutation (rs1049353) and Implications—A Cross-sectional Study

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ABSTRACT

Background: Considering the effects of environmental factors and genetic predispositions on mental health outcomes, the current work concentrated on the cannabinoid receptor 1 (CNR1) gene single-nucleotide polymorphism (SNP) rs1049353 as one of the primary genetic markers for cannabis-induced psychosis (CIP). By analyzing this SNP, the study contributes to the corpus of information to identify genetic traits that ultimately predict the response of an evolving disease following exposure to a particular substance after gene and environmental interaction and risk of a particular disease.

Methods: Grouped by CIP, cannabis use without psychosis, schizophrenia unlinked to cannabis use, and a healthy control group, a thorough investigation was conducted on a cohort of 120 patients at SCB Medical College, Cuttack. Standardized data collection within a cross-sectional study framework included socio-demographic profiles and genetic tests.

Results: Demographic analysis showed no significant differences in education, marital status, religion, occupation, housing, and family type between the groups. Genetic analysis done by real-time polymerase chain reaction (RT-PCR) to detect the prevalence of the CNR1 gene polymorphism among CIP patients was found to be 27.3% (95% CI: 12.1%–42.5%) for the heterogeneous allele and 72.7 % (95% CI: 57.5%–87.9%) for the homogenous allele. CIP patients showed a significant rise in homogenous allele expression in comparison to schizophrenia cases (*p* value: <.01; chi-square test).

Conclusions: The study found that a major contribution to the CIP risk in the CNR1 gene is an SNP, rs1049353. This result helps justify the need to include genetic elements in individual risk of developing a particular disease by linking gene and environmental interaction in cannabis related psychosis and accordingly the treatment plans and public health policy.

Keywords: Cannabis sativa, cannabinoid receptor 1(CNR1) gene, pharmacogenomics, cannabis-induced psychosis (CIP), single-nucleotide polymorphism (SNP) rs1049353

Key messages:

- The primary objective of this work was to underline the significance of the cannabinoid receptor 1 (CNR1) gene single-nucleotide polymorphism (SNP) rs1049353 as a major genetic marker for cannabis-induced psychosis (CIP).
- The study underlines the need to use genetic elements in customized medical treatments and public health campaigns. More importantly, it emphasizes the need to address genetic susceptibilities to identify the best strategies to avoid and treat those more susceptible to acquiring CIP.
- More investigation is needed to clarify the environmental and genetic elements causing psychosis.

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Historically considered a medical plant, cannabis sativa has two active chemical compounds, such as tetrahydrocannabinol (THC) and cannabidiol.[1] These compounds have both therapeutic advantages and detrimental cognitive consequences, so they are connected to different results for human health and behavior. The prevalence of cannabis use in the age group of 10–75 years in the eastern part of India is 4.5%, as per the National Drug Use Survey done by the Government of India.[2] Research by Wig and Varma (1977),[3] Agrawal and Lynskey (2009),[4] and Chopra and Smith (1974),[5] have shown the negative consequences of long-term cannabis use on mental health and cognitive abilities, particularly in the Indian setting.

Cannabis-induced psychosis (CIP) has an etiology that combines environmental and genetic elements in a complicated manner. The fact that just a small fraction of cannabis users, according to recent studies, experience psychosis highlights genetic sensitivity. Research by Zammit et al. (2007) found that differences in the cannabinoid receptor 1 (CNR1) gene are linked to a stronger reaction to THC and a higher risk of experiencing psychosis.[6] More research on these gene-environment interactions is essential, as they greatly affect the molecular processes causing psychosis in some people.[7]

Moreover, the interaction of environmental exposures and genetic susceptibilities greatly increases the risk of developing CIP. By influencing the brain's reward and addiction pathways, the CNR1 gene, which codes for the cannabinoid receptor type 1 (CB1), plays a significant role in modifying the neuropsychological effects of cannabis.[8] Some people respond differently to the pleasurable effects of THC and have varying risks of developing CIP, which has been linked to specific versions of the CNR1 gene, including the rs1049353 single-nucleotide polymorphism (SNP).[9] The CB1 receptor is encoded by the CNR1 gene located at the 6q14-q15 level, and the CB1 receptor, the protein found in the brain, plays a significant role in the neurobiology of CIP by modulating neurotransmitter release and influencing neuronal excitability; the rs1049353 SNP, a genetic variation in it, is considered a risk factor for increased susceptibility to CIP and schizophrenia, though results have been mixed.[10,11]

The endocannabinoid system includes two main types of receptors, called CB1 and CB2, along with the endocannabinoid compounds 2-arachidonoylglycerol and anandamide, as well as all the enzymes and processes involved. THC, the main psychoactive component of cannabis, is a partial agonist of the CB1 receptor. THC agonism at the CB1 receptor induces many of the subjective effects of cannabis, including sedation, analgesia, anti-emesis, and psychotropic effects. The rs1049353 and rs2023239 polymorphisms are among the best-characterized CNR1 polymorphisms; only a handful of studies have focused on them.[11]

Thoroughly treating CIP calls for a multifaceted strategy, including personal predispositions, self-medication behavior, and complex neurochemical processes.[12] Research advances suggest that the endocannabinoid system, in concert with dopaminergic signaling pathways, greatly fuels the pathogenesis of psychosis, therefore underscoring the intricate interactions between cannabis use and the beginning of psychotic diseases.[13] Clarifying the exact link between cannabis consumption and psychosis is dependent on both empirical and genetic studies, which are essential for the evolution of educated public health policies and focused treatments.[14,15]

The goal of this study was to examine how the CNR1 gene variation, particularly the rs1049353 SNP, is related to CIP. The study aimed to find out how common the specific SNP is in patients with CIP and to compare it with those who have cannabis dependence and schizophrenia, as well as to look at how the SNP affects the severity of cannabis use.

Methods

Study Setting

The investigation was conducted at the Department of Psychiatry of 2SCB Medical College, Cuttack a tertiary care hospital. Genetic analyses were carried out within the multidisciplinary research unit (MRU) at the medical college and hospital, with the approval of the Institutional Ethics Committee. The study spanned from September 2019 to November 2020, a period that included data collection and genetic laboratory work. This was a hospital-based cross-sectional study involving both outpatient and in-patient services of the psychiatric department. To investigate the frequency of the CNR1 gene polymorphism, four separate groups were established for comparison. In all the groups, participants were selected through purposive sampling within the age range of 18–60 years, excluding those with intellectual disabilities, any general medical disorders, and those who did not give informed consent. History was gathered from the participants and their caregivers, and mental status examinations were done. At least two independent psychiatrists made diagnoses using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria.

Group Co included patients diagnosed with CIP and excluded those with a family history of psychotic disorders and use of substances apart from cannabis. The C1 group comprised patients with the diagnosis of cannabis use disorder, but excluded those who developed CIP and those who used other substances except tobacco. The C2 group included patients diagnosed with schizophrenia who had never used cannabis, and the C3 group included normal individuals without any history of cannabis use or any psychotic disorder. The details of the study, including the need for collecting venous blood samples under aseptic conditions, were explained to all the study participants or their caregivers, and any queries were addressed. We obtained their informed consent before their participation.

Data Collection

We gathered socio-demographic and clinical data using a semi-structured proforma, which covered age, gender, marital status, socioeconomic status, education, religion, and residence.

Substance Use Assessment

The World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST),[16] helped classify drug use in groups Co and C1 as low, moderate, or high risk. ASSIST values were indicative of the phenotypic expressions of the CNR1 gene polymorphism in terms of risk score.

Gene Polymorphism Analysis

Using the Puregene DNA Isolation Kit (Gentra, Minneapolis, USA), a venous blood sample yielded genomic DNA (gDNA). We strictly adhered to the manufacturer's guidelines in obtaining the gDNA. This involved a multi-step extraction and purification process from RBC lysis, nucleated cell centrifugation, contaminant removal, and Nano Drop™ spectrophotometer quantification of the DNA concentration to yield high-quality gDNA. SNP genotyping was done using the TaqMan® SNP Genotyping Assay System. The wet DNA method of real-time polymerase chain reaction (RT-PCR) was used. PCR amplification was tracked in real-time with a 5-plex Rotor-Gene Q RT-PCR machine to evaluate genotyping accuracy throughout all cycles. Final, the post-PCR reading and analysis were done.

Two allele-specific fluorescent dye-labeled-TaqMan® MGB probes, VIC™ and FAM™, were employed to detect specific alleles of interest in the gDNA. If one VIC™-labeled probe detected the allele 1 sequence, the other was detected by using the FAM™-labeled probe in a DNA sequence. The SNP occurs at the [T/C] position within the sequence AACCGTGTGA[T/C]GGCAGTGATT. The VIC™-labeled probe detected the allele with T, whereas the FAM™-labeled probe detected the C-containing SNP allele. In this way, the genetic analysis resulted in scatter plots, which helped determine whether the alleles are heterozygous or homozygous.

Statistical Analysis

IBM Statistical Package for the Social Sciences statistics, version 21.0.0.0, was used for data entry and statistical analysis. Descriptive statistics were used for socio-demographic variables. The frequencies of the categorical variables in socio-demographic characteristics were calculated, whereas for age, the mean and standard deviation were calculated. Comparisons between the groups were done using chi-square tests and one-way ANOVA. Pearson's correlation coefficient was used to determine the correlations, with two-tailed significance at 0.05.

Results

Socio-demographic Profiles

Table 1 summarizes the socio-demographic traits of the 120 research participants spread among four groups: C0, C1, C2, and C3. Participants' ages ranged from C3, the oldest (mean 30.90 ± 7.49 years), to C1, the youngest (mean 26.07 ± 7.67 years). With the lower middle class making up 45.5% in C0 and 40.0% in C2, the lower middle class and

TABLE 1.

Socio-demographic Profile of Study Participants in C0, C1, C2, and C3 Groups (N = 120).

Variables	Category	C0 (*N* = 33) *n* (%)	C1 (*N* = 27) *n* (%)	C2 (*N* = 30) *n* (%)	C3 (*N* = 30) *n* (%)	*p* Value
Age (Mean ± *SD*)		28.39 ± 5.23	26.07 ± 7.67	30.33 ± 8.07	30.90 ± 7.49	.053*
Gender	Male	30 (90.0)	24 (88.9)	25 (83.3)	27 (90)	.832#
	Female	3 (9.1)	3 (11.1)	5 (16.7)	3 (10)	
Socioeconomic status	Upper	0 (0)	0 (0)	0 (0)	2 (6.7)	.738#
	Upper middle	3 (9.1)	1 (3.7)	4 (13.3)	3 (10)	
	Lower middle	15 (45.5)	10 (37.0)	12 (40.0)	11 (36.7)	
	Upper lower	14 (42.4)	16 (59.3)	14 (46.7)	14 (46.7)	
	Lower	1 (3.0)	0 (0)	0 (0)	0 (0)	
Education	Illiterate	1 (3.0)	0 (0)	0 (0)	0 (0)	.781#
	Primary	8 (24.2)	5 (18.5)	3 (10.0)	5 (16.7)	
	Secondary	11 (33.3)	10 (37.0)	13 (43.3)	12 (40.0)	
	Higher secondary	13 (39.4)	12 (44.4)	12 (40.0)	11 (36.7)	
	Graduate/postgraduate	0 (0)	0 (0)	2 (6.7)	2 (6.7)	
Marital status	Married	14 (42.4)	11 (40.7)	17 (56.7)	17 (56.7)	.437
	Unmarried	19 (57.6)	16 (59.3)	13 (43.3)	13 (43.3)	
Religion	Hindu	33 (100)	27 (100)	29 (96.7)	30 (100)	.725#
	Muslim	0 (0)	0 (0)	1 (3.3)	0 (0)	
Occupation	Unskilled	8 (24.2)	4 (14.8)	3 (10)	4 (13.3)	.627#
	Semiskilled	24 (72.7)	20 (74.1)	23 (76.7)	22 (73.3)	
	Skilled	1 (3.1)	3 (11.1)	2 (6.7)	2 (6.7)	
	Professional	0 (0)	0 (0)	2 (6.7)	2 (6.7)	
Domicile	Urban	10 (30.3)	12 (44.4)	13 (43.3)	12 (40.0)	.819#
	Rural	20 (60.6)	11 (40.7)	14 (46.7)	14 (46.7)	
	Semi urban	3 (9.1)	3 (10.0)	3 (10.0)	4 (13.3)	
Family type	Nuclear	14 (42.4)	16 (59.3)	9 (30.0)	11 (36.7)	.170
	Joint	16 (48.5)	7 (25.9)	13 (43.3)	11 (36.7)	
	Extended	3 (9.1)	4 (14.8)	8 (26.7)	8 (26.6)	

*One-way ANOVA test was used.
#: Fisher's Freeman Halton exact test was applied as the expected value <5 in at least 20% of the cells.
In other variables, the chi-square test was applied.

higher lower class were the most often occurring socioeconomic labels across all groupings. Both C1 at 59.3% and C3 at 46.7% primarily represented the upper and lower classes. Across all groups, the gender distribution was predominantly male; female representation gradually rose from Co (minimal) to C3 (16.7%).

Genotypes for CNR1 Gene SNP rs1049353

The distribution of SNP rs1049353 of the CNR1 gene among the research groups showed interesting differences, as seen in **Table 2**. The group with CIP mostly had the homozygous genotype (61.5%), while the schizophrenia group mainly had the heterozygous genotype (59.2%), indicating a possible genetic risk linked to CIP. The risk of getting a heterozygous allele in the CIP group is 98.7% less in comparison to the schizophrenia group (odds ratio: 0.013; 95% C.I.: 0.002–0.109).

CNR1 Gene Mutation: Genomic Analysis

Significant differences in the CNR1 gene have been found in several groups, especially between individuals with schizophrenia and CIP patients (*p* value: <.01; chi-square test), as shown in **Table 3**. Unlike the schizophrenia group, where it was low (3.3%), the homozygous CC genotype was dominant in the CIP group (72.7%; 95% CI: 57.5%–87.9%). This variation suggests a significant correlation between the CNR1 gene mutation and the occurrence of CIP.

Table 4 compared the genotypic expression of the CIP group with the phenotypic data assessed by the ASSIST score. We found no significant correlation between the two variables. This implied that the severity of cannabis use patterns is not influenced by polymorphism in the CNR1 gene. CNR1 gene SNP rs1049353 genotypic distribution scatter plot analysis (**Figure 1**).

TABLE 2.

Distribution of Genetic Expression of the CNR1 Gene Among Co, C1, C2, and C3 Groups.

Group	Normal *n* (%)	Heterozygous *n* (%)	Homozygous *n* (%)
Co	0 (0)	9 (18.4)	24 (61.5)
C1	0 (0)	11 (22.4)	14 (35.9)
C2	0 (0)	29 (59.2)	1 (2.6)
C3	30 (100)	0 (0)	0 (0)

TABLE 3.

Comparison of SNP rs1049353 of the CNR1 Gene in Co With C1 ands C2 Groups.

	Allele			
Group	Heterozygous *n* (%)	Homozygous *n* (%)	χ^2 value	*p* Value
Cannabis-induced psychosis	9 (27.3)	24 (72.7)	1.762	.184
Cannabis-induced dependence	11 (44.0)	14 (56.0)		
Cannabis-induced psychosis	9 (27.3)	24 (72.7)		
Schizophrenia	29 (96.7)	1 (3.3)	31.615	<.0001

χ^2: Chi-square value.

TABLE 4.

Comparison of Phenotypic Characteristics with Genotype Among CIP Group.

	ASSIST Score			
Allele	Mean	*SD*	*SE*	*p* Value
Heterozygous	24.44	3.43	1.14	.573
Homozygous	25.67	6.04	1.23	

The scatter plot analysis visually displays the allelic distribution of SNP rs1049353 within the CNR1 gene across the research cohorts. This study successfully showed the apparent differences in genotype frequencies between the groups. Compared to the schizophrenia group (shown in **Figure 2**), the scattered data points revealed a notable frequency of the CC homozygous genotype in the CIP and dependency groups.

Discussion

The genomic revolution has significantly expanded the potential of genetic findings to reinvent conventional diagnostic frameworks through studies on the interaction between genes, environments, and epigenetic events, creating new areas of genetics that play a major role in the management of psychiatric disorders.[17–19] Focusing especially on the rs1049353 polymorphism within the CNR1 gene, this study examined the role of this gene in the study population regarding susceptibility to CIP by utilizing modern SNP analysis techniques on DNA microarrays.[20,21] Our findings show that CNR1 rs1049353 homozygous status is associated with CIP in the study population, suggesting that it plays a role in the development of CIP. This is the first genetic analysis study on a cannabis-using population in India. In recent years, many studies have emphasized this polymorphism in the CNR1 gene through genetic analysis studies.[19,22–24]

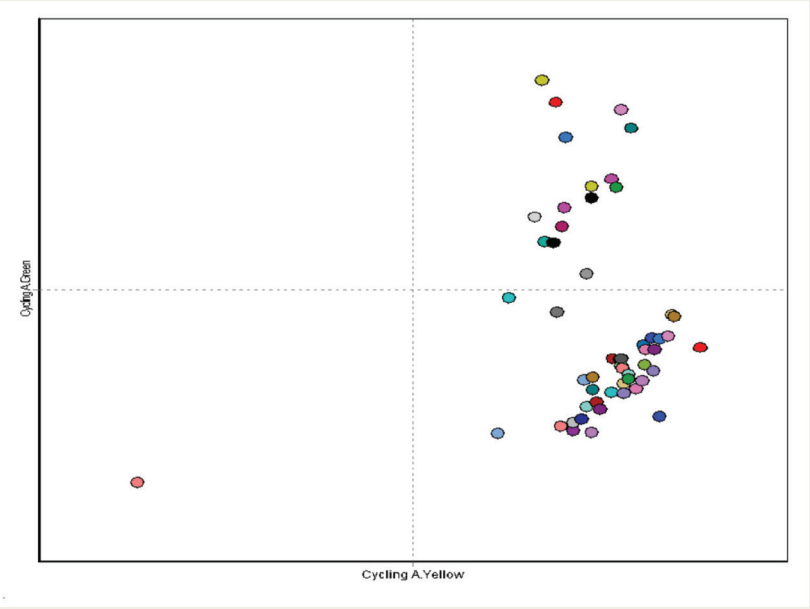
This study found that the CNR1 gene variant, like the rs1049353 SNP, has a significant association with CIP among cannabis users, where 61% prevalence of the CC homozygous CNR1 rs1049353 SNP in the CIP group, and 59% prevalence of the TC heterozygous CNR1 rs1049353 SNP in the schizophrenia group. It is a novel finding in the Indian population, as this has not been observed in any other recent studies. This finding needs to be replicated in a larger (Indian) population and other regions of the world, to ascertain its diagnostic and predictive values,[15,17,19] There is no other published CNR1 study in the cannabis-dependent population in India, which adds to the future research on the genetics of CIP.

Limitations and Future Implications

The limitation of our study is the small sample size of each study group. We did

FIGURE 1.

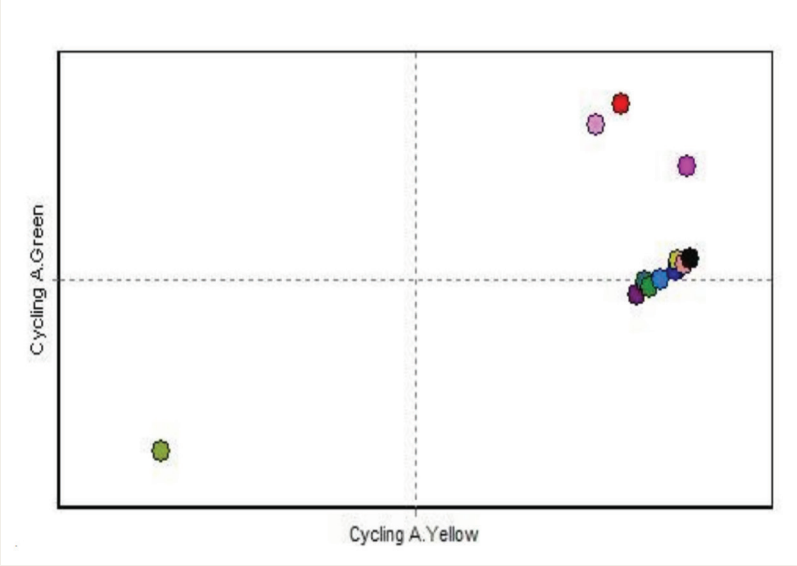
Scatter Plot of 60 CIP and Dependence Cases.



A green channel intensity on the Y-axis against a yellow channel intensity on the X-axis.
Quadrants represent genotypes: Upper left: Homozygous TT, Lower left: No Amplification, Upper right: Heterozygous CT, Lower right: Homozygous CC.

FIGURE 2.

Scatter Analysis Report of Schizophrenia Group Scatter Graph for Cycling A.



Green (Y-axis) Cycling A,Yellow (X-axis).

not use any laboratory marker or biological marker for recent cannabis use; instead, we relied upon self-reporting information, which can be subject to recall bias. Again, women were underrepresented in the study.

Although larger samples are required to elucidate the origins of CIP, future research should emphasize longitudinal studies and encompass a broader demographic spectrum to clarify the complex links between cannabis use and CIP, as well as to validate medications based on genetic risk assessment. Future research should integrate the causal association between SNPs and CIP, given the significant implications of these discoveries, to gain genomic insights into CIP. Our study findings can have the potential to aid in diagnosis and distinguish between CIP and schizophrenia with cannabis use. In addition, this can also help in the development of a personalized treatment plan.

Conclusions

The CNR1 rs1049353 SNP has been studied in various populations, except for Indians; however, no significant association between this genetic polymorphism and cannabis use (or CIP) has been established to date. In this novel study conducted in India, we genotyped the CNR1 gene variant rs1049353 and analyzed its correlation with CIP.

Our findings indicate that the CNR1 gene variant, specifically the rs1049353 SNP, is significantly associated with CIP among cannabis users, suggesting that it plays a role in the development of CIP within this population. Furthermore, we observed no significant association between the homozygous or heterozygous state of the CNR1 rs1049353 SNP and the consequences of cannabis use.

The study concludes that CNR1 polymorphism is not only significantly associated with cannabis dependence and CIP but also effectively distinguishes CIP from independent psychosis. However, it remains unknown whether a similar significant difference would be observed when comparing CIP and schizophrenia with occasional cannabis use. This is a unique aspect of our research.

Thus, a more rational future direction would involve replicating these findings within the Indian population and in other regions.

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Consent to Participate

Informed consent was obtained from participants who were willing in the written form in the prescribed format given below.

Consent for Publication

Not applicable.

Data Availability Statement

Data will be shared on a reasonable request.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Declaration Regarding the Use of Generative AI

None used.

Ethics Committee Details

Committee name: Institutional Ethics Committee, SCB MCH Cuttack, Odisha (Reg. No. ECR/84/INST/OR/2013/RR-20).

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