DOI: 10.7860/JCDR/2022/52129.15810

Original Article

Genetics Section

MU-Opioid Receptor (*OPRM1*) Gene Polymorphism and its Association with Alcohol Dependence: A Single Centre Study from Southern India

NAVINA SURESH[1], SUVARNA JYOTHI KANTIPUDI[2], K SANDHYA[3], SATHIANATHAN RAMANATHAN[4]

ABSTRACT

Introduction: Asn40Asp Opioid Receptor (*OPRM1*) polymorphism of the *MU-OPRM1* gene has been widely studied with regard to its association with alcohol dependence however results have been conflicting with evidence of ethnicity mediated effects.

Aim: To examine the association between *OPRM1* polymorphism and alcohol dependence in patients of South Indian ethnicity.

Materials and Methods: This cross-sectional study was conducted at Department of Psychiatry, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, Tamil Nadu, India, from November 2018 to May 2019. Cross-sectional assessments and peripheral venous blood genotyping were done in 50 male South Indian participants attending a tertiary care psychiatric setting. Clinical parameters such as severity of dependence and craving were assessed in addition to the subject's *OPRM1* genotype. The data collected was analysed using Statistical Package for the Social Sciences (SPSS) version 20.0.

Results: The mean age of the subjects was 39.62±8.50 years. This study showed a statistically significant association between alcohol dependence and the *OPRM1* polymorphism Asn40Asp among the study subjects (p-value <0.05). Furthermore, there was a higher than expected prevalence of the polymorphism of 86% among patients. However, there was no significant association between the polymorphism and clinical phenotypes such as severity of dependence or craving.

Conclusion: This study indicates a possible role of *OPRM1* polymorphism in alcohol dependence in South Indian patients and warrants further research with larger sample sizes. The association if replicated will shed light on aspects of aetiopathogenesis as well as have implications on treatment.

Keywords: Asn40Asp, Craving, G allele

INTRODUCTION

Alcohol dependence is a complex, multifactorial disorder and one of the most common substance use disorders. Decades of research have gone into understanding and elucidating the underlying aetiopathogenesis and neurobiological basis of alcohol dependence. While significant progress has been made with regard to understanding the neurobiological substrates and circuitry involved in alcohol addiction, much is still unknown regarding the genetic components and mechanisms involved. Initial studies revealing significant familial aggregation [1,2] pointed towards an underlying genetic basis for the disease process and of late, more research has been focused in this direction. Despite environmental factors playing an important role in alcohol dependence risk, twin and family based studies have demonstrated a heritability of approximately 50% [3].

Several genetic association studies have focused on allelic variation in *OPRM1* as a possible candidate locus for several alcoholism-related phenotypes [4]. The *OPRM1* gene encodes the *MU-OPRM1* which is a member of the G protein-coupled receptor family. The *MU-OPRM1* plays a key role in in several physiological functions such as pain perception, stress responsivity, immune function and addiction. The most common Single Nucleotide Polymorphism (SNP) of *OPRM1* gene, the Asn40Asp SNP(rs17799971), has received significant attention in view of molecular evidence that this locus codes for a protein site of glycosylation and can have functional significance [4]. There is an amino acid change in this variant, from asparagine to aspartic acid, which is thought to increase receptor binding affinity for beta-endorphin [5]. The Asn40Asp substitution polymorphism of the human *MU-OPRM1* (*OPRM1*, rs1799971) influences the opioid binding and signal transduction and could therefore contribute to the development of alcohol use disorder [5-7]. While this polymorphism seems to be functional, the evidence is contradictory regarding whether the minor allele (Asp40) is associated with a gain or loss of receptor function [8].

The *OPRM1* A118G polymorphism is associated with a 3 fold increased binding affinity of endogenous opioid beta endorphins and 3 fold increased current across G-protein activated inwardly rectifying potassium channels following binding by beta-endorphins [4]. However, in vitro transfection studies though showing a clear functional effect have however shown the G allele to be associated with decreased *OPRM1* protein expression with A118 yielding 10 fold more binding sites than G118 [8-10]. G118 substitution appears to affect translation, post-translational processing and turnover of *OPRM1* protein [8]. Also, previous studies have found the polymorphism to be associated with altered physiological response mediated by *MU-OPRM1* such as stress response [5,11,12]. Furthermore in other studies, A118G has been linked to difference in the pharmacological properties of *OPRM1*, where healthy volunteers with the polymorphism were found to exhibit increased Hypothalamic-Pituitary-Adrenal (HPA) axis response following administration of naloxone [13,14]. Since, both acute alcohol administration and *MU-OPRM1* antagonism stimulate HPA axis activity it was hypothesised that the 118G variant of the gene with the polymorphism acts in the development/treatment of alcoholism via HPA axis mediated mechanisms. Increased HPA axis activity and increased plasma cortisol have shown to be correlated with decreased craving. The precise molecular and functional consequences of this mutation remain unclear, but findings in animal models, human laboratory studies, and some but not all clinical trials indicate that *OPRM1* 118G allele confers elevated alcohol reward and is associated with the development of alcohol dependence [11-13]. Multiple studies have been conducted to test this association among different

populations however results have not been equivocal with some studies supporting an association while others did not. One of the reasons proposed for this was the allele frequency imbalance among population groups of different ethnicities and a possible ethnicity mediated effect. Amongst Indian literature, two studies conducted in Rajasthan and Kolkata respectively, both showed an association between the polymorphism and alcohol dependence [15,16].

This study aimed to find the proportion of South Indian males with *OPRM1* polymorphism in *MU-OPRM1* gene and to examine the association between *OPRM1* polymorphism and alcohol dependence in a sample of subjects of South Indian ethnicity attending the centre as there is dearth of literature examining the same in Southern India.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Department of Psychiatry, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai, Tamil Nadu, India, from November 2018 to May 2019. The study was approved by Sri Ramachandra Institute of Higher Education and Research Institutional Ethics Committee which adheres to Indian Council of Medical Research guidelines for biomedical research in human beings (IEC.No: 17/OCT/136/37). Initial sample comprised of 50 subjects recruited from outpatient and inpatient unit of Department of Psychiatry. Purposive sampling method was used to induct patients into the study.

Inclusion criteria: Male subjects of South Indian ethnicity in the age group of 18 to 60 years having ability to provide informed consent were included in the study.

Exclusion criteria: Patients with any other substance dependence except alcohol and tobacco dependence and patients suffering with any advanced neurological, cardiac, renal, hepatic, chronic infectious or debilitating disorder, or intellectual disability were excluded from the study.

Tools

1 Socio-demographic and clinical profile sheet

2) Diagnostic Criteria for Research accompanying the International Classification of Diseases-10 (DCR-10) for alcohol dependence, 10th revision [17].

3) Severity of Alcohol Dependence Questionnaire (SADQ) [18]

4) Obsessive Compulsive Drinking Scale (OCDS) [19]

5) Qiagen DNeasy Blood and Tissue Kit (50) for DNA purification and extraction, TaqMan SNP genotyping assay and Real Time PCR system (Assay ID C_ _ _8950074_1_1) for genotyping [20]. A 1.25 µL of a 20X combined primers and probe mix were added to 12.5 µL of a 2x TaqMAn Universal PCR master mix in a 25 µL final volume of DNAse/RNAse-free water and template and each allele was tagged using a fluorescent probe (VIC and FAM). Software used for analysis of raw data was Sequence Detection System (SDS) Software version 2.4 (Taqman Genotyper software).

STATISTICAL ANALYSIS

The data was analysed using Statistical Package for Social Scientists version 20.0 (SPSS). Discrete variables were computed as frequency and percentage. Mean and standard deviation was calculated for all the continuous variables. Chi-square test was used to compute the association between *OPRM1* polymorphism and alcohol dependence. Significance level was set at p-value ≤0.05. Odds ratio was calculated for 95% confidence interval.

RESULTS

Socio-demographic characteristics of subjects with and without alcohol dependence are presented under tables in [Table/Fig-1]. The subjects were more or less equally distributed with respect to religion, socio-economic status, marital status and habitat. The mean age of the subjects was 39.62±8.50 years. [Table/Fig-2] showing clinical characteristics of patients with alcohol dependence.

Variables	n (%)
Age (Mean±SD, years)	39.62±8.50
Religion	
Hindu	45 (90%)
Christian	4 (8%)
Other	1 (2%)
Habitat	
Urban	33 (66%)
Rural	17 (34%)
Socio-economic status	
Upper middle	5 (10%)
Lower middle	31 (62%)
Upper Lower	13 (26%)
Lower	1 (2%)
Marital status	
Married	37 (74%)
Single	9 (18%)
Other	4 (8%)

[Table/Fig-1]: Socio-demographic characteristics of the subjects.

Variables	Mean±SD (years)
Age at initiation	21.73±3.88
Time taken to reach dependent pattern of drinking	6.99±4.11
Duration of drinking	15.87±6.36
Duration of dependent pattern of drinking	8.16±6.11
Prior treatment for deaddiction	n (%)
Yes	18 (60%)
No	12 (40%)
Family history of alcohol dependence	
Yes	21 (70%)
No	9 (30%)

[Table/Fig-2]: Clinical characteristics of patients with alcohol dependence (N=30).

Frequency of G allele in subjects with and without alcohol dependence:

$$\text{Frequency of Gallele of the individual} = \frac{\text{Number of copies of G allele}}{\text{Total number of copies of gene in population}}$$

In the present study, there were 55 copies of G allele out of 100 copies of gene in the study population which makes the subject G allele frequency as 0.55 or 55%. Furthermore in the study, authors calculated G allele frequency in both groups separately. The result showed that the G allele frequency was 0.65 or 65% in subjects with alcohol dependence and G allele frequency was 0.40 or 40% in subjects without alcohol dependence. Overall, the G allele frequency was higher in the former group.

***OPRM1*genotype and association with alcohol dependence:** Authors genotyped for 3 *OPRM1* variants namely AG/GA, GG, AA and examined the 'presence of any G allele' genotype, that is, AG/GA/GG variants. The presence of any G allele and GG genotype was more prevalent among patients who had alcohol dependence than patients with no alcohol dependence.

These associations were statistically analysed using Chi-square test. The results showed statistically significant positive association between prevalence of any G allele (AG/GA/GG) genotype with patients with alcohol dependence at a significance level of p-value <0.05. Similarly it was also found that, statistically significant negative association between AA genotype and patients with alcohol dependence at a p-value of <0.05. In this study, among 30 subjects with alcohol dependence syndrome, any G allele genotype was present in 26

patients and AA genotype present only in four patients. The prevalence of the polymorphism in subjects with and without alcohol dependence is shown in [Table/Fig-3] and the association between genotype and alcohol dependence is shown in [Table/Fig-4].

OPRM1 Genotype	Subjects with Alcohol Dependence (N=30) N (%)	Subjects without Alcohol Dependence (N=20) N (%)
AG/GA	13 (43.3)	8 (40)
GG	13 (43.3)	4 (20)
Any G allele	26 (86.6)	12 (60)
AA	4 (13.3)	8 (40)

[Table/Fig-3]: Prevalence of OPRM1 polymorphism in subjects with and without alcohol dependence.

Allele		Subjects with Alcohol Dependence (N=30)	Subjects without Alcohol Dependence (N=20)	Chi-Square Value	Odds Ratio
AG/GA	Yes	13	8	0.055	
	No	17	12		
GG	Yes	13	4	2.911	
	No	17	16		
AA	Yes	4	8	4.678*	0.231
	No	26	12		
Any G AG/GA/GG	Yes	26	12	4.678*	4.33
	No	4	8		

[Table/Fig-4]: Association between genotype and alcohol dependence.
*p-value ≤0.05

There was a statistically significant association between having GG genotype and family history of alcohol dependence, but there were no significant associations between any of the other genotypes and family history of alcohol dependence [Table/Fig-5]. There was no statistically significant association between any of the SADQ or OCDS scale items or total scores with the *OPRM1* genotype. The SADQ and OCDS scale scores and mean scores are shown in [Table/Fig 6,7].

GG Genotype	Family History Present (N=21)	Family History absent (N=9)	Chi-Square Value	Odds Ratio
Yes	12	1	5.436*	10.667
No	9	8		

[Table/Fig-5]: Association between GG genotype and family history of alcohol dependence.
*p-value ≤0.05

SADQ Total Score (N=30)	n (%)
Severity of dependence on SADQ	n (%)
Mild dependence (less than 16)	10 (33.3)
Moderate dependence (16 to 30)	19 (63.3)
Severe dependence (>31)	1 (3.3)
Total score (Mean±SD)	20.40±8.12

[Table/Fig-6]: Severity of alcohol dependence as measured by SADQ total score.

Obsessive Compulsive Drinking Scale (OCDS)	Mean±SD
Obsessive subscale	9.77±3.06
Compulsive subscale	12.37±2.68
OCDS total score	22.13±5.22

[Table/Fig-7]: Mean scores of OCDS (N=30).

DISCUSSION

Broadly Indians belong to Austro-Asiatic, Tibeto-Burman, Indo-European and Dravidian language families (Indian Genome Variation Consortium). As Indian population is not genetically homogenous, in the present study authors sought to examine the possible association between *OPRM1* A118G polymorphism and alcohol dependence in the Dravidian population. Therefore, all of the subjects in the current study were South Indians who were of Dravidian ethnicity.

In this study, the frequency of occurrence of *OPRM1* polymorphism, defined as presence of any G allele, was higher in subjects with alcohol dependence. Studies in the past reported that the estimated prevalence rate in Asian populations range between 40% and 50%. In this study, 86.6% of alcohol dependent subjects had any G allele as compared to 60% of those without alcohol dependence. This is comparable to a previous study done in Eastern India [21] which shows frequency of occurrence of any G allele (AG/GA/GG) of 70% in alcohol dependent individuals, and 46% in normal controls. In the current study, the G allele frequency for alcohol dependent subjects was 0.65 and for other subjects it was 0.40. This was higher than frequencies observed in another study by Kapur S et al., where the G allele frequency was 0.31 in opiate dependents and 0.12 in control group [15], however they did not study the alcohol dependent population. The G allele frequency in the Asian population was estimated to be 0.31-0.43 [22]. The minor allele frequency obtained in various studies conducted till date is elucidated below [Table/Fig-8] [21,23-39]. The occurrence of this polymorphism in the South Indian population as per our study is clearly higher than that estimated in Asians however further research with larger sample sizes is warranted to reconcile the disparate findings within the Indian population and find definitive occurrence rates. It is possible that India being a genetically heterogenous mosaic of various sub-ethnicities and geographical groups, there may be difference in occurrence rates within the country in various regions.

In the present study, it was also observed that the homozygous expression of G allele that is GG genotype was significantly much higher in the alcohol dependent patients (43.3%) than in controls (20%) while the converse was true for AA homozygous expression genotype, with control group having higher prevalence of 40% than alcohol dependent patients who had 13.3%. This indicates likely effect of *OPRM1* polymorphism on alcohol dependence. Statistical tests of association yielded significant association between any G allele genotype (AG/GA/GG) and presence of alcohol dependence. This was in line with the previous studies conducted in this area in India [16,17]. It also aligns with previous functional neuroimaging findings such as G allele carriers displaying enhanced striatal dopamine release in response to intravenously infused alcohol [40] and G allele carriers demonstrating greater cue-elicited activation of ventral striatum, orbitofrontal cortex, medial prefrontal cortex/anterior cingulate, inferior frontal gyrus and claustrum than A homozygotes [41]. In the current study, estimated odds ratio for any G allele with presence of alcohol dependence was 4.33 which can be interpreted as patients with G allele or *OPRM1* polymorphism being four times more likely to have alcohol dependence than those without.

In a 2016 meta-analysis of European ancestry cohorts which analysed the *OPRM1* variant's association with non specific liability to substance dependence (the substances included were alcohol, opioids, cannabis, cocaine and nicotine), they found that the G allele was inversely associated with substance dependence [42]. This was contradictory to the present study findings. It could possibly be ethnicity mediated due to the significantly lower G allele frequency in cases which varied from 0.09 to 0.20 in the European ancestry cohort as compared to the present study South Indian subject G allele frequency of 0.65. The fact of our relatively small sample size can also not be overlooked. Other reasons could be due to interaction with other population specific genetic/ environmental factors. Interactions are strongly likely in a complex disorder such as addiction and said to possibly attenuate the genetic main effect when not accounted for especially when the effect occurs only in a specific stratum. For example, in one study, among naltrexone treated subjects, G allele carriers who were also homozygous for DAT1 10-repeat allele of the DA transporter gene (DAT1/SLC6A3) had reduced drinking relative to placebo while A allele homozygotes who carried the DAT1 9-repeat allele had greater drinking [43].

Author, year *OPRM1*, Rs17999971	Country	Ethnicity	MAF cases/controls (G variant)	Sample Size cases/controls	Genotype cases/controls GG	Genotype cases/controls GA/AG	Genotype cases/controls AA
Bergen AW et al., 1997 [23]	United States of America	Finnish Caucasian	0.165/0.113	88/182	2/1	25/39	61/142
		South West American Indian	0.164/0.153	116/108	4/2	30/29	82/77
		US Caucasian	0.025/0.125	20/80	0/0	1/20	19/60
Sander T et al., 1998 [24]	Germany	German	0.078/0.107	327/340	4/2	62/49	261/289
Franke P et al., 2001 [25]	Germany	Caucasian	NA	221/365	1/7	50/74	170/284
		Caucasian	NA	75/75	0/2	20/16	55/57
Schinka JA et al., 2002 [26]	USA	Caucasian	0.093/0.175	91/63	0/4	21/73	87/220
Kim SA et al., 2004 [27]	Korea	Korean	0.31/0.37	100/128	7/21	47/53	46/54
Kim SG et al,2004 [28]	Korea	Korean	0.397/0.311	112/140	14/15	61/57	37/68
Loh EW et al., 2004 [29]	Taiwan	Taiwanese Han	NA	146/154	18/20	77/55	58/70
Zhang H et al., 2005 [30]	USA	European-American	0.120/0.129	318/338	4/4	68/78	245/256
Nishizawa D et al., 2006 [31]	Japan	Japanese	0.52/0.43	64/74	15/15	37/33	12/26
Deb I et al., 2010 [21]	India	Indian	0.396/0.280	53/82	5/8	32/30	16/44
Koller G et al., 2012 [32]	Germany	German	0.112/0.127	1845/1863	31/27	353/419	1461/1417
Cupic B et al., 2013 [33]	Croatia	Caucasian	0.117/0.133	354/357	4/4	75/87	275/266
Rouvinen-Lagerstrom N et al., 2013 [34]	Finland	Finnish	NA	409/506	26/29	152/157	325/320
Frances F et al., 2015 [35]	Spain	Caucasian	NA	630/133	15/2	190/30	425/101
Jin JD and JH P 2015 [36]	China	Chinese	NA	58/50	5/2	12/9	41/39
SC Gurel et al., 2016 [37]	Turkey	Turkish	0.026/0.030	121/117	2/1	22/28	97/88
Ragia G et al., 2016 [38]	Greece	Greek	0.118/0.108	72/74	0/1	17/14	55/59
Samochowiec A et al., 2019 [39]	Poland	Polish	0.14/0.09	162/177	2/3	29/40	146/119

[Table/Fig-8]: Minor Allele Frequencies (MAF) and genotypes of OPRM1 gene in previous studies [21,23-39].

Other mediating influences could be environmental such as social and religious norms, availability of alcohol, political and cultural attitudes towards drinking indigenous to the population being studied [18], age and other epistatic effects. Hence, gene-gene and gene-environment interactions also need to be considered and future studies are required to examine and identify possible such interactions.

In our study, there was a significant negative association between AA genotype and presence of alcohol dependence (p-value<0.05). Among 30 subjects with alcohol dependence, *OPRM1* polymorphism was present in 26 patients while AA genotype was present only in 4 patients. From the results of our current study, we can surmise that it is possible that *OPRM1* polymorphism has an effect upon risk of alcohol dependence and merits further study with adequate sample sizes.

We also studied the polymorphism in relation to family history of alcohol dependence. Positive family history was defined as having a first degree relative with history of alcohol dependence. Out of 30 subjects with alcohol dependence, 21 had a positive family history of alcohol dependence out of which 19 had one or more G alleles while 12 had homozygous expression of G allele (GG). There was a statistically significant association between family history of alcohol dependence with GG genotype (p-value<0.05) which points towards familial genetic loading and contribution of the G allele to heritability of the disorder. The estimated odds ratio for GG alleles in genotype with family history of alcohol dependence was 10.7 indicating that subjects with homozygous GG genotype were close to 11 times more likely to have a family history of alcohol dependence.

Another two statistically significant associations were found between presence of AA genotype and consumption of more than one bottle of spirits per day in SADQ as well as amount of control over drinking in OCDS scale. The latter association might point towards lower craving in the AA genotype as indicated by previous functional findings. Overall, while the study revealed a significant association between *OPRM1* polymorphism and alcohol dependence syndrome, there was no significant effect of the polymorphism on clinical phenotypes.

Limitation(s)

As the study sample was from a tertiary care hospital setting of subjects attending psychiatry department, there may have been sampling bias, therefore the findings may not be suitable for extrapolation to the general population. Since the scales administered were subjective in nature, there may have been testing bias. Previous studies have shown that *OPRM1* A118G polymorphism contributes to mechanisms of addiction liability that are shared across different addictive substances. This study however did not include other commonly used substances such as nicotine, use of which frequently co-occurs with alcohol dependence.

CONCLUSION(S)

This study revealed a statistically significant association between the *OPRM1* polymorphism of *MU-OPRM1* gene and alcohol dependence. There was also a statistically significant association between homozygous expression of the polymorphism and positive family history of alcohol dependence. These findings are supportive of a likely association between this MU- *OPRM1* gene polymorphism and alcohol dependence in South Indians which needs to be further studied.

Acknowledgement

The first author receives funding from ICMR under the ICMR-TSS fellowship programme. The authors would like to acknowledge the contributions by Dr. M. Suresh Kumar and Dr. M. S. Karthik towards advice in conducting and carrying out the study.

REFERENCES

[1] Kendler KS, Prescott CA, Neale MC, Pedersen NL. Temperance board registration for alcohol abuse in a national sample of Swedish male twins, born 1902 to 1949. Arch Gen Psychiatry. 1997;54(2):178-84.
[2] Prescott CA, Kendler KS. Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. Am J Psychiatry. 1999;156(1):34-40.

[3] Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychol Med. 2015;45(5):1061-72.
[4] Ray LA, Barr CS, Blendy JA, Oslin D, Goldman D, Anton RF. The role of the Asn40Asp polymorphism of the mu opioid receptor gene (OPRM1) on alcoholism etiology and treatment: a critical review. Alcohol Clin Exp Res. 2012;36(3):385-94.
[5] Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, et al. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. Proc Natl Acad Sci U S A. 1998;95(16):9608-13.
[6] Goldman D, Oroszi G, O'Malley S, Anton R. COMBINE genetics study: the pharmacogenetics of alcoholism treatment response: genes and mechanisms. J Stud Alcohol Suppl. 2005;(15):56-64.
[7] Anton RF, Oroszi G, O'Malley S, Couper D, Swift R, Pettinati H, et al. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry. 2008;65(2):135-44.
[8] Zhang Y, Wang D, Johnson AD, Papp AC, Sadée W. Allelic expression imbalance of human mu opioid receptor (OPRM1) caused by variant A118G. J Biol Chem. 2005;280(38):32618-24.
[9] Beyer A, Koch T, Schröder H, Schulz S, Höllt V. Effect of the A118G polymorphism on binding affinity, potency and agonist-mediated endocytosis, desensitization, and resensitization of the human mu-opioid receptor. J Neurochem. 2004;89(3):553-60
[10] Kroslak T, LaForge KS, Gianotti RJ, Ho A, Nielsen DA, Kreek MJ. The single nucleotide polymorphism A118G alters functional properties of the human mu opioid receptor. J Neurochem. 2007;103(1):77-87.
[11] Kreek MJ, Nielsen DA, LaForge KS. Genes associated with addiction. Neuromolecular Med. 2004;5(1):85-108.
[12] LaForge KS, Yuferov V, Kreek MJ. Opioid receptor and peptide gene polymorphisms: potential implications for addictions. Eur J Pharmacol. 2000;410(2-3):249-68.
[13] Wand GS, McCaul M, Yang X, Reynolds J, Gotjen D, Lee S, Ali A. The mu-opioid receptor gene polymorphism (A118G) alters HPA axis activation induced by opioid receptor blockade. Neuropsychopharmacology. 2002;26(1):106.
[14] Hernandez-Avila CA, Wand G, Luo X, Gelernter J, Kranzler HR. Association between the cortisol response to opioid blockade and the Asn40Asp polymorphism at the μ-opioid receptor locus (OPRM1). Am J Med Genet B Neuropsychiatr Genet. 2003;118(1):60-65.
[15] Kapur S, Sharad S, Singh RA, Gupta AK. A118g polymorphism in mu opioid receptor gene (oprm1): association with opiate addiction in subjects of Indian origin. J Integr Neurosci. 2007;6(04):511-22.
[16] Kumar D, Chakraborty J, Das S. Epistatic effects between variants of kappa-opioid receptor gene and A118G of mu-opioid receptor gene increase susceptibility to addiction in Indian population. Prog Neuropsychopharmacol Biol Psychiatry. 2012;36(2):225-30.
[17] World Health Organization. The ICD-10 Classification of mental and behavioural disorders: Diagnostic criteria for research. World Health Organization; 1993.
[18] Stockwell T, Hodgson R, Edwards G, Taylor C, Rankin H. The development of a questionnaire to measure severity of alcohol dependence. Br J Addict Alcohol Other Drugs. 1979;74(1):79-87.
[19] Anton RF, Moak DH, Latham PK. The obsessive compulsive drinking scale: A new method of assessing outcome in alcoholism treatment studies. Arch Gen Psychiatry. 1996;53(3):225-31.
[20] Jia, Y. Chapter 3-Real-Time PCR. In Methods in Cell Biology; Laboratory Methods in Cell Biology; Conn, P.M., Ed.; Academic Press: Cambridge, MA, USA, 2012; Volume 112, pp. 55–68.
[21] Deb I, Chakraborty J, Gangopadhyay PK, Choudhury SR, Das S. Single-nucleotide polymorphism (A118G) in exon 1 of OPRM1 gene causes alteration in downstream signaling by mu-opioid receptor and may contribute to the genetic risk for addiction. Journal of Neurochemistry. 2010;112(2):486-96.
[22] Nishizawa D, Han W, Hasegawa J, Ishida T, Numata Y, Sato T, Kawai A, Ikeda K. Association of μ-opioid receptor gene polymorphism A118G with alcohol dependence in a Japanese population. Neuropsychobiology. 2006;53(3):137-41.
[23] Bergen AW, Kokoszka J, Peterson R, Long JC, Virkkunen M, Linnoila M, Goldman D. μ opioid receptor gene variants: lack of association with alcohol dependence. Mol Psychiatry. 1997;2(6):490-94.
[24] Sander T, Gscheidel N, Wendel B, Samochowiec J, Smolka M, Rommelspacher H, et al. Human μ-opioid receptor variation and alcohol dependence. Alcohol Clin Exp Res. 1998;22(9):2108-10.
[25] Franke P, Wang T, Nöthen MM, Knapp M, Neidt H, Albrecht S, et al. Nonreplication of association between μ-opioid-receptor gene (OPRM1) A118G polymorphism and substance dependence. American Journal of Medical Genetics. 2001;105(1):114-19.
[26] Schinka JA, Town T, Abdullah L, Crawford FC, Ordorica PI, Francis E, et al. A functional polymorphism within the μ-opioid receptor gene and risk for abuse of alcohol and other substances. Mol Psychiatry. 2002;7(2):224-28.
[27] Kim SA, Kim JW, Song JY, Park S, Lee HJ, Chung JH. Association of polymorphisms in nicotinic acetylcholine receptor α4 subunit gene (CHRNA4), μ-opioid receptor gene (OPRM1), and ethanol-metabolizing enzyme genes with alcoholism in Korean patients. Alcohol. 2004;34(2-3):115-20.
[28] Kim SG, Kim CM, Kang DH, Kim YJ, Byun WT, Kim SY, et al. Association of functional opioid receptor genotypes with alcohol dependence in Koreans. Alcohol Clin Exp Res. 2004;28(7):986-90.
[29] Loh EW, Fann CS, Chang YT, Chang CJ, Cheng AT. Endogenous opioid receptor genes and alcohol dependence among Taiwanese Han. Alcohol Clin Exp Res. 2004;28(1):15-19.
[30] Zhang H, Luo X, Kranzler HR, Lappalainen J, Yang BZ, Krupitsky E, et al. Association between two μ-opioid receptor gene (OPRM1) haplotype blocks and drug or alcohol dependence. Human Molecular Genetics. 2006;15(6):807-19.
[31] Nishizawa D, Han W, Hasegawa J, Ishida T, Numata Y, Sato T, et al. Association of μ-opioid receptor gene polymorphism A118G with alcohol dependence in a Japanese population. Neuropsychobiology. 2006;53(3):137-41.
[32] Koller G, Zill P, Rujescu D, Ridinger M, Pogarell O, Fehr C, et al. Possible association between OPRM 1 genetic variance at the 118 locus and alcohol dependence in a large treatment sample: relationship to alcohol dependence symptoms. Alcohol Clin Exp Res. 2012;36(7):1230-36.
[33] Cupic B, Stefulj J, Zapletal E, Matosic A, Bordukalo-Niksic T, Cicin-Sain L, et al. Opioid system genes in alcoholism: A case-control study in Croatian population. Neuropeptides. 2013;47(5):315-19.
[34] Rouvinen-Lagerström N, Lahti J, Alho H, Kovanen L, Aalto M, Partonen T, et al. μ-Opioid receptor gene (OPRM1) polymorphism A118G: lack of association in Finnish populations with alcohol dependence or alcohol consumption. Alcohol and Alcoholism. 2013;48.
[35] Francés F, Portolés O, Castelló A, Costa JA, Verdú F. Association between opioid receptor mu 1 (OPRM1) gene polymorphisms and tobacco and alcohol consumption in a Spanish population. Bosn J Basic Med Sci. 2015;15(2):31.
[36] Jin JD, JH P. Relationship between A118G polymorphism of OPRM1 gene and alcohol dependence. China Journal of Modern Medicine. 2015;25(3):07-10.
[37] Gurel SC, Ayhan Y, Karaaslan C, Hayriye AK, Karaca Ro, Babaoglu Mo, et al. [mu]-Opioid Receptor Gene (OPRM1) polymorphisms A118G and C17T in alcohol dependence: A Turkish sample. Turk Psikiyatri Dergisi. 2016;27(2).
[38] Ragia G, Veresies I, Veresie L, Veresies K, Manolopoulos VG. Association study of DRD2 A2/A1, DRD3 Ser9Gly, DβH– 1021C> T, OPRM1 A118G and GRIK1 rs2832407C> A polymorphisms with alcohol dependence. Drug Metabolism and Personalized Therapy. 2016;31(3):143-50.
[39] Samochowiec A, Samochowiec J, Pełka-Wysiecka J, Kucharska-Mazur J, Grochans E, et al. The role of OPRM1 polymorphism in the etiology of alcoholism. Advances in Clinical and Experimental Medicine. 2019;28(2):199-202.
[40] Ramchandani VA, Umhau J, Pavon FJ, Ruiz-Velasco V, Margas W, Sun H, et al. A genetic determinant of the striatal dopamine response to alcohol in men. Mol Psychiatry. 2011;16(8):809.
[41] Filbey FM, Ray L, Smolen A, Claus ED, Audette A, Hutchison KE. Differential neural response to alcohol priming and alcohol taste cues is associated with DRD4 VNTR and OPRM1 genotypes. Alcohol Clin Exp Res. 2008;32(7):1113-23.
[42] Schwantes-An TH, Zhang J, Chen LS, Hartz SM, Culverhouse RC, Chen X, et al. Association of the OPRM1 variant rs1799971 (A118G) with non-specific liability to substance dependence in a collaborative de novo meta-analysis of European-ancestry cohorts. Behav Genet. 2016;46(2):151-69.
[43] Schacht JP, Anton RF, Voronin KE, Randall PK, Li X, Henderson S, et al. Interacting effects of naltrexone and OPRM1 and DAT1 variation on the neural response to alcohol cues. Neuropsychopharmacology. 2013;38(3):414

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Psychiatry, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
2. Associate Professor, Department of Psychiatry, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
3. Psychiatric social worker, Department of Psychiatry, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
4. Professor and Head, Department of Psychiatry, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Suvarna Jyothi Kantipudi,
Flat.no:30,Staff quarters,F-Block Sri Ramachandra College Campus, Porur,
Chennai-600116, Tamil Nadu, India.
E-mail: suvarna.srmc@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 27, 2021
- Manual Googling: Oct 06, 2021
- iThenticate Software: Oct 07, 2021 (14%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: Funded by ICMR under the ICMR-TSS fellowship programme
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 26, 2021**
Date of Peer Review: **Oct 11, 2021**
Date of Acceptance: **Nov 21, 2021**
Date of Publishing: **Jan 01, 2022**