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Association of ADH1C and ALDH2 genes with alcohol dependence in south Indian Tamilian population: A case control approach

Umamageswari Arunachalam. MD.
Professor, Department of Pharmacology,T agore Medical College and Hospital, Rathinamangalam, Vandalur, Chennai, Tamilnadu, India. 600127
ORCID ID: 0000-0003-0912-191X
*Corresponding author email: leeuma6@gmail.com

Aarthi Manoharan, PhD.
Research Scientist, Multidisciplinary Center for Biomedical Research, Vinayaka Mission's Research Foundation, Aarupadai Veedu Medical College,Puducherry, India. 607402
ORCID ID: 0000-0003-2318-2786
Email: aarthi1231@gmail.com

Iyanar Kannan, PhD.
Associate Professor, Department of Microbiology, Tagore Medical College and Hospital, Rathinamangalam, Vandalur,Chennai, Tamilnadu, India. 600127
ORCID ID: 0000-0002-3575-1264
Email: dr.ikannan@tagoremch.com

Adithan Chandrasekaran, MD, PhD
Former Dean Research, Sri Balaji Vidyapeeth, Pillaiyarkuppam, Puducherry, India. 607402
ORCID ID: 0000-0002-0109-6441
Email: adithan50@gmail.com

***Abstract*---**Objectives: Alcohol dependence (AD) poses a serious medical problem and significant public health issue contributing to morbidity and mortality throughout the world. The aim of the study was to establish the allele and genotype frequencies and to test the association of rs698 (ADH1C) and rs671(ALDH2) with the risk of alcohol dependence in south Indian Tamilian population. Methodology: A total of 150 alcohol dependent cases aged between 18- and 65-years fulfilling DSM-V criteria were recruited from the de-addiction centre. Blood donors (n=150) who had a history of alcohol intake with AUDIT score of less than eight were selected for the control group. The alleles were genotyped using TaqMan SNP

genotyping assays by quantitative PCR. Association with alcohol dependence was evaluated with various genetic models using the Chi-square test. Multiple logistic regression analysis was performed to explore the effect of covariates. Results: The observed genotype frequency distributions of rs698 and rs671 were in agreement with Hardy Weinberg equilibrium (p>0.05).The dominant and allelic genetic model of ALDH2, rs671 between cases and controls showed a statistically significant association of the genetic variant with AD. Multivariate logistic regression analysis revealed family history and cigarette smoking were significantly associated with AD but there was no association between rs671 genotypes in the presence of these co-variates. Conclusions: The present study found a significant association between rs671 and alcohol dependence in the south Indian Tamilian population but not between rs698 and AD. Combined analysis of functional genetic variants and associated factors is warranted in future studies.

***Keywords*---**alcohol dependence, ADH1C polymorphism, ALDH2 polymorphism, genotyping, Tamilian population.

Introduction

Alcohol dependence (AD) is a multifactorial chronic relapsing behavioral disorder and a major public health problem[1]. Heterogeneity in alcoholism is influenced by genetic factors and further moderated by environmental and social factor[2]. Findings from many families, adoption, and twin studies on alcoholism revealed that genetic factors play a considerable role in the development of AD where risk proportion ranges from 40 to 60% in both males and females[3,4]. Alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase (*ALDH*) are the primary enzymes responsible for the metabolism of ethanol. The *ADH* and *ALDH* isoforms that determine the levels of acetaldehyde in the body are mainly implicated in the etiology of alcoholism and drinking behavior[5].The aversive effects of acetaldehyde such as facial flushing, nausea and tachycardia reduce the dependence of alcohol and protect against alcoholism[5,6]. A more active *ADH* and a less active *ALDH* may lead to higher accumulation of acetaldehyde in the blood resulting in “flushing syndrome”. Genetic variants in these genes are modifiers of risk of alcoholism[7,8].

The *ADH1C* belongs to class I of human *ADH* genes cluster on chromosome 4q21 and is responsible for about 70% of total ethanol oxidation[5,9].The largest genome-wide association study (GWAS) identified the *ADH1B/ADH1C* region to be associated with the risk of alcoholism[10]. *ADH1C*2*associated variants rs698 (Ile350Val) and rs1693482 (Arg272Gln) which are in very high linkage disequilibrium with each other have been shown to modify the risk of AD mostly in east Asians[11,12]. *ADH1C*1*Ile350 ‘T’ allele which is widely prevalent (about 90%) in Asians has higher enzyme activity about twice the enzyme activity of *ADH1C*2*, and is found to be protective in Chinese and Koreans[12,13].

The *ALDH2* gene located on chromosome 12q24.2 encodes the mitochondrial isozyme *ALDH2*, highly expressed in stomach and liver and is significantly involved in the oxidation of acetaldehyde[14].The functional polymorphism rs671, G>A, Glu504Lys also referred to as *ALDH2*2* exhibits lower enzyme activity. The mutant protective allele *ALDH2*2* Lys504 is commonly distributed among Asians ranging in frequency between 12 to 41% [5,15]. Individuals homozygous for this variant have no enzyme activity and heterozygous individuals show 30 to 50% activity[16]. Previous reports have consistently shown the protective effect of *ALDH2*2* in east Asians[17-19]. Genetic variants of *ADH1C* and *ALDH2* were demonstrated to be significantly associated with AD especially in east Asian population including a meta-analysis[12,19-21].The association between the well-documented variants rs698 and rs671 is much less explored especially in south Indian population. The aim of the present study is to establish the allele and genotype frequencies of rs698 and rs671 and also to test for association between these two SNPs and AD in the south Indian Tamilian population.

Methods

Subjects

Our study was a case control approach, wherein 150 male subjects satisfying Diagnostics and Statistical Manual (DSM)-V criteria for AD, aged between 18 and 65 years were recruited from the de-addiction centre. The controls consisted of 150 male blood donors with exposure to alcohol but no alcohol use disorder/abuse as evaluated by DSM V as well as Alcohol Use Disorders Identification Test (AUDIT)[22] a useful questionnaire for the identification of harmful drinking. All the subjects in the control group had AUDIT score of less than eight. Subjects with substance abuse disorder (other than nicotine) and psychiatric illnesses such as schizophrenia, bipolar disorder and, major depressive disorder were excluded by an expert psychiatrist. The study period was from September 2018 to December 2020. All subjects were of self-reported Tamilian ancestry.

The study was approved by the Institutional Ethics Committee and all the subjects provided written informed consent. Two ml of venous blood was collected from the subjects. DNA was isolated using the spin column-based DNA extraction kit (QIAamp DNA Blood Mini Kit, Qiagen, Hilden, Germany) according to the manufacturer's instructions.The study achieved the required sample size considering power at 80% and α (Type I error probability) at 0.05, calculated using the minor allele frequency (MAF) of least prevalent SNP in other Indian sub-populations which was rs671 A allele with a frequency of 19% in a north Indian population[23].

Genotyping

Quantitative PCR was performed using 5' exonuclease fluorescence TaqMan SNP genotyping assay kits (Applied Biosystems, Foster City, CA, USA) for rs698 (assay ID: C_26457410_10) and rs671(C_11703892_10). The real-time polymerase chain reaction protocol comprised of initial denaturation at 95 °C for 10 min, followed by 50 cycles of denaturation at 95 °C for 15s, annealing & extension at 60 °C for

90s. The assays were run on Bio-Rad CFX96 Real-Time PCR Detection System (Biorad Laboratories, CA, USA). Allelic discrimination was carried out using CFX Maestro Software 2.0 (Biorad Laboratories, CA, USA). TaqMan genotyping was performed using 50ng of DNA, 5 µL of the GoTaq® Probe qPCR Master Mix 2X (Promega Corporation, USA), 0.5 µL TaqMan assay 40X, and 2.5µL of Nuclease-free water. The accuracy of genotyping was confirmed by randomly rerunning 15% of the samples.

Statistical analysis

Demographic variables were compared between cases and controls using Chi-square test for nominal variables and Student's *t*-test for continuous variables. Fisher's exact test was used to test if the observed genotype frequencies were in Hardy-Weinberg equilibrium. Allele and genotype frequencies were calculated by direct gene counting method. Association with AD was evaluated with dominant, co-dominant recessive and additive genetic models using Chi-square test. Binary logistic regression was used to explore the combined effect of rs698 and rs671 alleles on AD. For this analysis, the total number of risk (rs698 'C", rs671 'G') alleles and protective (rs698 'T', rs671 'A') alleles was calculated for each individual. Each subject therefore had either four risk alleles or four protective alleles or two risk and two protective alleles or three risk alleles and one protective allele and vice versa. Multiple logistic regression was performed considering significantly associated variant from univariate analysis and co-variates such as age, family history and cigarette smoking. Statistical analyses were performed using SPSS version 20 (IBM SPSS statistics NY, USA) and GraphPad Prism version 9 (San Diego, CA, USA).

Results

The mean age (Mean ± SEM) of AD cases and controls was 37.69 ± 0.82 and 33.95 ± 1.09 years, respectively.The mean age at which first use of alcohol in both case and control group was 20 years. We found significantly more number of smokers and individuals with family history of AD among alcohol dependents. Table 1 & 2 shows the genotype and allele frequencies of the SNPs. The genotype frequencies of the SNPs were in Hardy-Weinberg Equilibrium (p=0.6242 for rs698; p=0.9327 for rs671). The dominant model of *ALDH2*, rs671 between cases and controls revealed a significant association of the genetic variant with AD. Similarly, the allelic association for rs671 also showed a significant association with AD (Table 3). However, the combined effect of risk and protective alleles did not show any significant association with AD. Multivariate logistic regression analysis showed that factors such as family history (OR, 95% CI: 3.04, 1.79-5.17), cigarette smoking (OR, 95% CI: 1.99, 1.24-3.21) remained significantly associated with AD but there was no association between rs671 genotypes in the presence of these co-variates.

Discussion

The present study shows the occurrence of the minor alleles of rs671 and rs698 at a frequency between 21.3% and 33.3% respectively in the south Indian Tamilian control population. The frequency of rs671 across Asian control

populations (24% Japanese, 27% southern Han Chinese, 36% Koreans, 30% Taiwanese) is found to be higher when compared to our study control population [24-26]. Interestingly, there exists a wide variation in MAF among five Chinese ethnic populations and the frequency of A allele ranges between 0.8% to 18.9% [27]. Among Indian populations, intriguingly a study reported Glu504 to be monomorphic in some Indian populations (Madhya Pradesh, Maharashtra and Andhra Pradesh) among healthy controls[28]. A similar result is observed with major global populations viz., the allelic variant is rare in African (0.2%), American (0.3%) and absent in European population[29].

In our study, the frequency of the *ALDH2*2* minor allele is found to be higher in alcoholics (30.3%) than the control group and there exists a statistically significant difference between these groups. A study involving only AD subjects of north Indian origin (n=174) established allele frequency at 19% which is lower than our study alcoholics. Furthermore, the study revealed high frequency of *ALDH2*2* among alcoholics and deemed it to be a risk factor for AD[23]. However, the amount of alcohol consumption in rs671 homozygous mutants was significantly lower compared to other genotypes. On the contrary, the strong protective effect of *ALDH2*2* against AD is evident from a meta-analysis consisting of 15 Asian studies (Korean, Chinese, Japanese) revealed an odd's ratio (OR) of 0.22 for *ALDH2*2* heterozygous (*1/*2:*1/*1) on genotype comparison[13]. Similarly, another comprehensive meta-analysis showed a very strong association of rs671 with AD and alcohol abuse in a dominant model[5]. The significant association between the decreased risk of AD and *ALDH2*2* has been shown in the Japanese population though the inactive allele is associated with increased risk for alcoholic polyneuropathy and cancer [21]. O'Shea et al. analyzed the relationship between *ALDH2*2* A allele and peer drunkenness interaction in east Asian college students confirming the strong protective effect of *ALDH2*2* against alcohol addiction [30].

More recently, a GWAS (including a discovery and replication cohort) in Han Chinese alcoholic dependents and controls revealed a significant association of *ALDH2* rs671 and *ADH1B* rs1229984 with AD. In addition, the study compared the polygenic risk scores from Thai, European American and African American with Han Chinese found to be significantly associated with AD[13]. Wu et al investigated 282 SNPs and 61 genes involved in alcohol metabolism pathways along with systems of dopamine, serotonin, GABA in Taiwanese subjects. A combined meta-analysis of family and case-control samples revealed three SNPs notably rs671, rs698 and rs1229984 were significantly associated with AD[31].

On comparing the control population, the MAF of rs698 in the present study is marginally higher than south west American Indians (n=72, 27%) and north Indians (n= 108, 25%) [11,32]. Across the major global populations, the frequency of this allele is seen at 50% in Caucasians and 15% in African Americans and is the least frequent in east Asians[11,13,27]. In our study, minor allele G is found to be slightly higher in alcoholics than control population though there is no significant difference seen in the allele frequencies between these groups. Similarly, an earlier Indian study reported lack of association between rs698 and alcoholism with a considerable frequency of the minor allele at 32% in north Indian population[33]. Borras et al., also reported no association between AD and

*ADH1C*1* in European individuals[34]. These reports are contradictory, since the protective effect of Ile350 against risk of AD is consistently reported in different Asian populations[35,36] than in non-Asian populations[19,37]. However, in a Turkish study, rs698 was not associated with AD whereas rs1229984 (Arg47His, also referred to as *ADH1B*2*) which is in high linkage disequilibrium with rs698 was associated with AD[38]. rs698 and the another allelic variant of *ADH1C*2* rs1693482 were found to be in high LD with rs1789891 (a SNP located between *ADH1B* and *ADH1C*) is significantly associated with AD[39]. There was significant association between *ADH1B* rs129984, *ADH1C* rs698, rs1693482 variants as well as *ADH1C-1B* intergenic markers and alcohol dependence syndrome in British and Irish population[40].The variants of the *ADH* cluster are in strong LD with each other to an extent that precludes the analysis of independent effect of these variants[40]. Since the *ADH1* genes are in close proximity with each other, different variants in each of these genes could influence alcoholic behavior[41].

In a study that analyzed the effect of *ADH* variants alongside religious involvement, rs698 was associated with higher alcohol consumption and AD symptoms with low or no religious involvement but not with higher religious involvement levels[42], suggesting the significant influence of social factors in modifying the genetic susceptibility. Hence, analysis of joint effect of different functional genetic variants in conjunction with non genetic factors will enable dissecting this complex behavioral disorder for better management and treatment in future studies.

Conclusion

The present study established allele and genotype frequencies of rs698 and rs671 in Tamilians, a population of south India.There was a statistically significant association between *ALDH2* and AD in both dominant and allelic genetic models. Meanwhile, no association was found between *ADH1C* and AD in the south Indian Tamilian population.

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Tables

Table 1
Comparison of genotype frequencies among alcohol dependent (N=150) and control (N=150) groups

SNP	Genotype	alcohol dependent %(n)	95%CI	Control %(n)	95%CI	P value
rs698 *ADH1C*	TT	38(57)	30.6-45.9	45(68)	37.5-53.3	0.32
	TC	47(70)	38.8-54.6	43(64)	35.0-50.6	
	CC	15(23)	10.4-21.9	12(18)	07.7-18.1	
rs671 *ALDH2*	GG	49(73)	40.8-56.5	62(93)	54.0-69.3	0.06
	GA	42(63)	34.3-50.0	33(50)	26.2-41.2	
	AA	09(14)	05.6-15.0	05(07)	02.2-09.3	

CI : Confidence Interval, N denotes number of subjects ; n denotes number of genotypes.

The p-values are obtained by comparing alcohol dependent and control groups, P value (<0.05) - significant.

Table 2
Comparison of allele frequencies among alcohol dependent (2N=300) and control (2N=300) groups

SNP	Allele	alcohol dependent %(n)	95%CI	Control %(n)	95%CI	P value
rs698 *ADH1C*	T	61.3(184)	55.7-66.6	66.7(200)	61.1-71.7	0.20
	C	38.7(116)	33.3-44.2	33.3(100)	28.2-38.8	
rs671 *ALDH2*	G	69.7(209)	64.2-74.5	78.7(236)	73.6-82.9	0.01
	A	30.3(91)	25.4-35.7	21.3(64)	17.0-26.3	

CI : Confidence Interval, N denotes number of subjects ; n denotes number of alleles.
The p-values are obtained by comparing alcohol dependent and control groups, P value (<0.05) - significant.

Table 3
Allelic and genotypic analysis of *ADH1C* and *ALDH2* among case and control groups

Models	OR (95% CI)	P value
rs698 (*ADH1C*)		
Dominant (TT Vs TC+CC)	0.739 (0.473 - 1.179)	0.24
Recessive (CC Vs TT+ TC)	1.328 (0.670 - 2.588)	0.50
Co dominant (TC Vs CC+TT)	1.176 (0.743 - 1.867)	0.56
Additive (CC Vs TT)	1.524 (0.744 - 3.013)	0.28
Allelic (C Vs T)	0.793 (0.566 - 1.106)	0.20
rs671 (*ALDH2*)		
Dominant (GG Vs GA+AA)	0.581 (0.372 - 0.922)	0.02
Recessive (AA Vs GG+GA)	2.103 (0.812 - 5.409)	0.17
Co dominant (GA Vs GG+AA)	1.448 (0.913 - 2.307)	0.15
Additive (GG Vs AA)	0.392 (0.154- 0.983)	0.06
Allelic	0.622 (0.432 - 0.901)	0.01

(G Vs A)		

Pearson's chi-squared test
CI – confidence interval, OR – odds ratio, P value (<0.05) - significant