Association between ALDH2 Variant and Alcohol Dependence in South Indian Population.

A Umamageswari  
Tagore Medical College and Hospital Department of Pharmacology

C Adithan  
Mahatma Gandhi Medical College and Research Institute

Aarthi Manoharan (✉ aarthi1231@gmail.com)  
Aarupadai Veedu Medical College & Hospital  https://orcid.org/0000-0003-2318-2786

Iyanar Kannan  
Tagore Medical College and Hospital

Research Article

Keywords: alcohol dependence, genotyping, single nucleotide polymorphism, Tamilian population

Posted Date: November 11th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1046349/v1

License: ☑️ This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Background:** 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 is to test the association of rs698 (ADH1C) and rs671 (ALDH2) with the risk of alcohol dependence and to further assess the influence of environmental factors on altering the genetic susceptibility to alcoholism in south Indian Tamilian population.

**Methods & Results:** A total of 150 alcohol dependent cases aged between 18- and 65-years fulfilling DSM-V criteria were recruited from de addiction center. Subjects in control group (n=150) had history of alcohol intake with AUDIT score less than 8. The alleles were genotyped using TaqMan SNP genotyping assays by quantitative PCR. Association with alcohol dependence was evaluated with various genetic models using chi-square test. Multiple logistic regression analysis was performed to explore the effect of covariates. The dominant (OR=0.5811, 95% CI: 0.372-0.9224, p<0.01) and allelic genetic model (OR=0.6228, 95% CI: 0.4328-0.9009, p<0.01) of ALDH2, rs671 between cases and controls showed a significant association of the genetic variant with AD. Multivariate logistic regression analysis revealed education level, family history, marital status were significantly associated with AD but there was no association between rs671 genotypes in the presence of these co-variates.

**Conclusions:** Genetic factors play an important role in alcohol dependence. Combined analysis of functional genetic variants and environmental factors is warranted in future studies.

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 [3] play a considerable role in the development of alcohol dependence where risk proportion ranges from 40 to 60% in both males and females[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[5,6]. The aversive effects of acetaldehyde such as facial flushing, nausea and tachycardia reduce the dependence of alcohol and protect against alcoholism [6–8]. 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 [9,10].

The ADH1C belongs to class I of human ADH genes cluster on chromosome 4q21 [11] and is responsible for about 70% of total ethanol oxidation [6,12]. The largest genome-wide association study (GWAS) identified the ADH1B/ADH1C region to be associated with the risk of alcoholism [13]. ADH1C*2-associated variants rs698 (Ile350Val) and rs1693482 (Arg272Gln) which are in very high linkage disequilibrium with
each other [14] have been shown to modify the risk of alcohol dependence mostly in East Asians [15,16]. ADH1C*1Ile350 ‘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 initially in Chinese and Koreans [15–17]. Later compelling evidence was produced by studies across European, American and African populations demonstrating the association between rs698 and alcohol dependence or abuse further corroborated by a meta-analysis [18].

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 [19]. 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% [6,20]. Individuals homozygous for this variant have no enzyme activity and heterozygous individuals show 30 to 50% activity [21]. Previous reports have consistently shown the protective effect of ALDH2*2 in east Asians [22–24].

Genetic variants of ADH1C and ALDH2 were demonstrated to be significantly associated with AD especially in East Asian population including a meta-analysis[15,24–26]. 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 test for association of the two rs698 and rs671 with the risk of alcohol dependence in south Indian Tamilian population as well as study the influence of environmental factors such as education level, employment and marital status on altering the genetic susceptibility to alcoholism.

**Methods**

**Subjects**

One hundred and fifty male subjects satisfying Diagnostics and Statistical Manual (DSM)-V criteria for alcohol dependence, aged between 18 and 65 years were recruited from de addiction centre (TTK Hospital, Chennai). Subjects with substance abuse disorder (other than nicotine) and psychiatric illnesses such as schizophrenia, bipolar disorder and, major depressive disorder were excluded. The controls consisted of 150 male subjects with exposure to alcohol but no alcohol use disorder/abuse as evaluated by DSM V as well as Alcohol Use Disorders Identification Test (AUDIT) [27], a useful questionnaire for the identification of harmful drinking where controls are defined by an AUDIT score of less than 8. All subjects were of self-reported Tamilian ancestry.

The study was approved by the Institutional Ethics Committee, Tagore Medical College and Hospital (TMCH), 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.
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 alcohol dependence 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 rs671 and rs698 alleles on AD. For this analysis, the total number of risk (rs671 ‘G’, rs698 ‘C’) alleles and protective (rs671 ‘A’, rs698 ‘T’) alleles was calculated for each individual. Each subject therefore had either 4 risk alleles or 4 protective alleles or 2 risk and 2 protective alleles or 3 risk alleles and 1 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, education level, employment and marital status.

Results

The demographic characteristics compared between cases and controls are shown in Table 1. We found significantly more educated subjects among controls while number of individuals who had a family history of AD, married and employed were significantly high among alcohol dependents. The study also shows a significantly greater number of smokers among alcohol dependents. Table 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 education level (adjusted OR, 95% CI: 6.34, 2.15-18.67), family history (adjusted OR, 95% CI: 2.97, 1.66-5.31), marital status (adjusted OR,
95% CI: 2.75, 1.3-5.78) 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 21-30% and 33-38% respectively in the south Indian study population. The frequency of rs671 across Asian populations (19% Japanese, 23 % Chinese, 36% Koreans) is quite similar to the frequencies observed in this south Indian population. Among Indian populations, intriguingly a study reported Glu504 to be monomorphic in some Indian populations (Madhya Pradesh, Maharashtra and Andhra Pradesh) [28] in healthy controls. However, Vaswani et al. found the *ALDH2*^2^ minor allele to be present at a frequency of 19% in a north Indian population which agrees with the finding of the present study [29]. The minor allele frequency of rs698 in this study population is marginally higher than north Indians (25%) and south West Indians (27%) [14,30]. Across the major global populations, the frequency of this allele is seen at 50% in Caucasians and 15% in African Americans [14] and is the least frequent in east Asians [16,31].

The present study found a significant rs671 allelic association with AD which was also reflected in the dominant genetic model. The strong protective effect of *ALDH2*^2^ against AD is well-established. A meta-analysis showed a very strong association of rs671 with alcohol dependence and alcohol abuse with an allelic p value of 3x10^{-56}. The study also showed significance with dominant model (lys-lys + lys-glu vs. glu-glu) concurring with the findings of the present study[6]. The significant association between the decreased risk of alcohol dependence and *ALDH2*^2^ has been shown in many Asian studies [23,26] including a meta-analysis that demonstrated the link between *ALDH2*^1^ and increased risk of AD according to a dominant model only in east Asians. O'Shea et al. analyzed the relationship between *ALDH2*^2^ A allele and peer drinking in east Asian college students confirming the strong protective effect of *ALDH2*^2^ against alcohol addiction [32]. In an Indian study though, in contrast to studies on Asian subjects, Vaswani et al. found a high frequency of *ALDH2*^2^ among north Indian alcohol dependent subjects and deemed it to be a risk factor. However, the amount of alcohol consumption in rs671 homozygous mutants was significantly lower compared to other genotypes [29].

More recently, a GWAS (including a discovery and replication cohort) in Han Chinese alcoholic dependents and controls and in their analysis of polygenic risk scores (PRS) derived from GWAS summary statistics with European American, African American and Thai population revealed the significant association of *ALDH2* rs671 and *ADH1B* rs1229984 with AD [33]. In a family-based association test in Taiwanese subjects followed by case-control study and a meta-analysis of both studies, rs671, rs698 and rs1229984 were significantly associated with AD among 282 SNPs and 61
genes involved in the systems of dopamine, serotonin, GABA, and alcohol metabolism [34]. Our study did not find any association between rs698 and AD. The combination of risk and protective alleles from rs671 and rs698 also showed no association with AD.

In an earlier Indian study that reported a considerable frequency of rs698 (about 35%) in north Indian population, no association was found between rs698 and alcoholism [35]. Borras et al., also reported no association between AD and ADH1C*1 in European individuals [8]. These reports are contradictory to many studies across major global populations where ADH1C*1, Ile350 has been shown to lower the risk of AD [18]. The protective effect Ile350 is consistently reported in different Asian populations [18,36] than in non-Asian populations [24,37–39] 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 [40]. rs1229984 is also highly prevalent in Asian population but is rarely seen in non-Asians [6,15,41]. rs1229984 is linked with the pathogenesis of alcohol dependence [42] and is protective against AD in different populations [22,42–44]. This functional variant encodes β2β2, a more active form of the enzyme that results in rapid oxidation of ethanol and higher concentrations of acetaldehyde [45,46]. It has been suggested that the protective effect of ADH1C*1 could be in part attributed to its strong LD with ADH1B*2 [6]. rs698 and the second allelic variant of ADH1C*2 rs1693482 were also found to be in high LD with rs1789891 which is significantly associated with AD and is located between ADH1B and ADH1C [47]. There was significant association between ADH1B rs129984 and ADH1C rs698, rs1693482 variants as well as ADH1C-1B intergenic markers and alcohol dependence syndrome in British and Irish population [48].

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 [48]. Since the ADH1 genes are in close proximity with each other, different variants in each of these genes could influence alcoholic behavior. The analysis of joint effect of ADH1C and ADH1B variants is warranted in future studies [49].

In a study that analyzed the effect of ADH variants alongside religious involvement, rs698 was associated with higher maximum drinks and more alcohol dependence symptoms with low or no religious involvement but not with higher religious involvement levels [50], suggesting the significant influence of social factors in modifying the genetic susceptibility. The results of the present study also show the significant influence of social and environmental factors such as family history of AD and level of education in modulating the risk of AD while diminishing the significance of genetic factors in influencing the susceptibility to AD.

**Conclusion**

The study has corroborated the genetic contribution of ALDH2*2 conferring protection against AD. However, AD is influenced by many gene-gene and gene environmental interactions. Analysis of joint
effect of different functional genetic variants in conjunction with environmental factors will enable dissecting this complex behavioral disorder for better management and treatment.

Declarations

Competing interests:

Authors state no conflict of interest.

Funding:

This study had received partial financial support as a research grant for the year 2019-2020 from The Tamilnadu Dr.MGR Medical University, Chennai, India.

Ethical approval and Informed consent:

The study protocol was approved by Institutional Ethics Committee of Tagore Medical College and Hospital. Written informed consent was obtained from the participants prior to commencement of the study.

Acknowledgment:

We would like to thank our study participants for their active participation and support.

References

1. He L, Deng T, Luo HS (2015) Genetic polymorphism in alcohol dehydrogenase 2 (ADH2) gene and alcoholic liver cirrhosis risk. Int J Clin Exp Med 8(5):7786–7793
2. Edenberg HJ, Foroud T (2013) Genetics and alcoholism. Nat Rev Gastroenterol Hepatol 10(8):487–494
3. Mayfield RD, Harris RA, Schuckit MA (2008) Genetic factors influencing alcohol dependence: Genetic factors and alcohol dependence. Br J Pharmacol 154(2):275–287
4. Tawa EA, Hall SD, Lohoff FW (2016) Overview of the Genetics of Alcohol Use Disorder. Alcohol Alcohol 51(5):507–514
5. Chao YC, Liou SR, Chung YY, Tang HS, Hsu CT, Li TK et al (1994) Polymorphism of alcohol and aldehyde dehydrogenase genes and alcoholic cirrhosis in chinese patients. Hepatology 19(2):360–6
6. Hurley TD, Edenberg HJ (2012) Genes Encoding Enzymes Involved in Ethanol Metabolism. Alcohol Res Curr Rev 34(3):339–344
7. Polimanti R, Gelernter J (2018) ADH1B: From alcoholism, natural selection, and cancer to the human phenome. Am J Med Genet B Neuropsychiatr Genet 177(2):113–25
8. Borrás E, Coutelle C, Rosell A, Fernande Muixi F, Broch M, Crosas B et al (2000) Genetic polymorphism of alcohol dehydrogenase in Europeans: The ADH2*2 allele decreases the risk for alcoholism and is associated with ADH3*1, vol 31. Hepatology, pp 984–989
9. Ehlers CL (2007) Variations in ADH and ALDH in Southwest California Indians. Alcohol Res Health 30(1):14–17
10. Anstee QM, Seth D, Day CP (2016) Genetic Factors That Affect Risk of Alcoholic and Nonalcoholic Fatty Liver Disease. Gastroenterology 150:1728–1744e78
11. Chen YC, Peng GS, Wang MF, Tsao TP, Yin SJ (2009) Polymorphism of ethanol-metabolism genes and alcoholism: Correlation of allelic variations with the pharmacokinetic and pharmacodynamic consequences. Chem Biol Interact 178(1–3):2–7
12. Lee SL, Höög JO, Yin SJ (2004) Functionality of allelic variations in human alcohol dehydrogenase gene family: assessment of a functional window for protection against alcoholism. Pharmacogenet Genomics 14(11):725–732
13. Clarke TK, Adams MJ, Davies G, Howard DM, Hall LS, Padmanabhan S et al (2017) Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117). Mol Psychiatry 22(10):1376–1384
14. Liu J, Zhou Z, Hodgkinson CA, Yuan Q, Shen PH, Mulligan CJ et al (2011) Haplotype-Based Study of the Association of Alcohol Metabolizing Genes with Alcohol Dependence in Four Independent Populations. Alcohol Clin Exp Res 35(2):304–316
15. Osier M, Pakstis AJ, Kidd JR, Lee JF, Yin SJ, Ko HC et al (1999) Linkage disequilibrium at the ADH2 and ADH3 loci and risk of alcoholism. Am J Hum Genet 64(4):1147–57
16. Shen YC, Fan JH, Edenberg HJ, Li TK, Cui YH, Wang YF et al (1997) Polymorphism of ADH and ALDH genes among four ethnic groups in China and effects upon the risk for alcoholism. Alcohol Clin Exp Res 21(7):1272–7
17. Osier MV, Pakstis AJ, Goldman D, Edenberg HJ, Kidd JR, Kidd KK (2002) A proline-threonine substitution in codon 351 of ADH1C is common in Native Americans. Alcohol Clin Exp Res 26(12):1759–1763
18. Li D, Zhao H, Gelernter J (2012) Strong protective effect of the aldehyde dehydrogenase gene (ALDH2) 504lys (*2) allele against alcoholism and alcohol-induced medical diseases in Asians. Hum Genet 131(5):725–737
19. Ramchandani VA, Bosron WF, Li TK (2001) Research advances in ethanol metabolism. Pathol Biol 49(9):676–682
20. Yin SJ, Peng GS (2005) Overview of ALDH polymorphism: relation to cardiovascular effects of alcohol. In: Preedy VR, Watson RR (eds) Comprehensive Handbook of Alcohol related Pathology. Elsevier Academic, London, pp 409–424
21. Kuo PH, Kalsi G, Prescott CA, Hodgkinson CA, Goldman D, van den Oord EJ et al (2008) Association of ADH and ALDH Genes With Alcohol Dependence in the Irish Affected Sib Pair Study of Alcohol Dependence (IASPSAD) Sample. Alcohol Clin Exp Res 32(5):785–795

22. Crabb DW, Matsumoto M, Chang D, You M (2004) Overview of the role of alcohol dehydrogenase and aldehyde dehydrogenase and their variants in the genesis of alcohol-related pathology. Proc Nutr Soc 63(1):49–63

23. Chai YG, Oh DY, Chung EK, Kim GS, Kim L, Lee YS et al (2005) Alcohol and aldehyde dehydrogenase polymorphisms in men with type I and Type II alcoholism. Am J Psychiatry 162(5):1003–1005

24. Zintzaras E, Stefanidis I, Santos M, Vidal F (2006) Do alcohol-metabolizing enzyme gene polymorphisms increase the risk of alcoholism and alcoholic liver disease? Hepatol Baltim Md 43(2):352–361

25. Cheng ATA, Gau SF, Chen THH, Chang JC, Chang YT (2004) A 4-year longitudinal study on risk factors for alcoholism. Arch Gen Psychiatry 61(2):184–191

26. Higuchi S, Matsushita S, Masaki T, Yokoyama A, Kimura M, Suzuki G et al (2004) Influence of genetic variations of ethanol-metabolizing enzymes on phenotypes of alcohol-related disorders. Ann N Y Acad Sci 1025:472–480

27. Babor TF, de la Fuente JR, Saunders J, Grant M (2011) The Alcohol Use Disorders Identification test: Guidelines for Use in Primary Health Care. Geneva, Switzerland:World Health Organization.WHO Publication No92.4

28. Bhaskar LVKS, Thangaraj K, Osier M, Reddy AG, Rao AP, Singh L et al (2007) Single nucleotide polymorphisms of the ALDH2 gene in six Indian populations. Ann Hum Biol 34(6):607–619

29. Vaswani M, Prasad P, Kapur S (2009) Association of ADH1B and ALDH2 gene polymorphisms with alcohol dependence: a pilot study from India. Hum Genomics 3(3):213–220

30. Ghosh S, Bankura B, Ghosh S, Saha ML, Pattanayak AK, Ghatak S et al (2017) Polymorphisms in ADH1B and ALDH2 genes associated with the increased risk of gastric cancer in West Bengal, India. BMC Cancer 17(782):1–11

31. Wei Q, Ye Y, Chen F, Li J, Wu H, Fu Y et al (2018) Polymorphism study of nine SNPs associated with subjective response to alcohol in Chinese Han, Hui, Tibetan, Mongolian and Uygur populations. Forensic Sci Res 3(2):124–9

32. O'Shea T, Thomas N, Webb BT, Dick DM, Kendler KS, Chartier KG (2017) )ALDH2 *2 and peer drinking in East Asian college students. Am J Drug Alcohol Abuse 43(6):678–685

33. Sun Y, Chang S, Wang F, Sun H, Ni Z, Yue W et al (2019) Genome-wide association study of alcohol dependence in male Han Chinese and cross-ethnic polygenic risk score comparison. Transl Psychiatry 9(1):249

34. Wu LSH, Lee CS, Weng TY, Wang KHT, Cheng ATA (2016) Association Study of Gene Polymorphisms in GABA, Serotonin, Dopamine, and Alcohol Metabolism Pathways with Alcohol Dependence in Taiwanese Han Men. Alcohol Clin Exp Res 40(2):284–290
35. Dutta AK (2013) Genetic factors affecting susceptibility to alcoholic liver disease in an Indian population. Ann Hepatol 12(6):901-7
36. Li D, Zhao H, Gelernter J (2012) Further Clarification of The Contribution of The ADH1C Gene to The Vulnerability of Alcoholism And Selected Liver Diseases. Hum Genet 131(8):1361–1374
37. Tolstrup JS, Nordestgaard BG, Rasmussen S, Tybj A, Grønb M (2008) Alcoholism and alcohol drinking habits predicted from alcohol dehydrogenase genes. Pharmacogenomics J 8:220–227
38. Tóth R, Fiatal S, Petrovski B, McKee M, Adány R (2011) Combined effect of ADH1B rs1229984, rs2066702 and ADH1C rs1693482/ rs698 alleles on alcoholism and chronic liver diseases. Dis Markers 31(5):267–277
39. Olfson E, Bierut LJ (2012) Convergence of Genome-Wide Association and Candidate Gene Studies for Alcoholism. Alcohol Clin Exp Res 36(12):2086–2094
40. Aktas EO, Kocak A, Senol E, Celik HA, Coskunol H, Berdeli A et al (2012) Determination of the effects of Alcohol Dehydrogenase (ADH) 1B and ADH1C polymorphisms on alcohol dependence in Turkey. Sci Justice 52(1):58–61
41. Choi IG, Son HG, Yang BH, Kim SH, Lee JS, Chai YG et al (2005) Scanning of genetic effects of alcohol metabolism gene (ADH1B and ADH1C) polymorphisms on the risk of alcoholism. Hum Mutat 26(3):224–234
42. Li D, Zhao H, Gelernter J (2011) Strong Association of The Alcohol Dehydrogenase 1B Gene (ADH1B) With Alcohol Dependence And Alcohol-induced Medical Diseases. Biol Psychiatry 70(6):504–512
43. Whitfield JB (2002) Alcohol dehydrogenase and alcohol dependence: variation in genotype-associated risk between populations. Am J Hum Genet 71(5):1247–1250
44. Ehlers CL, Liang T, Gizer IR (2012) ADH and ALDH polymorphisms and alcohol dependence in Mexican and Native Americans. Am J Drug Alcohol Abuse 38(5):389–394
45. Goedde HW, Agarwal DP, Fritze G, Meier-Tackmann D, Singh S, Beckmann G et al (1992) Distribution of ADH2 and ALDH2 genotypes in different populations. Hum Genet 88(3):344–6
46. Mizoi Y, Yamamoto K, Ueno Y, Fukunaga T, Harada S (1994) Involvement of genetic polymorphism of alcohol and aldehyde dehydrogenases in individual variation of alcohol metabolism. Alcohol Alcohol 29(6):707–710
47. Treutlein J, Frank J, Streit F, Reinbold C, Juraeva D, Degenhardt F et al (2017) Genetic Contribution to Alcohol Dependence: Investigation of a Heterogeneous German Sample of Individuals with Alcohol Dependence, Chronic Alcoholic Pancreatitis, and Alcohol-Related Cirrhosis. Genes 8(7):183
48. Way M, McQuillin A, Saini J, Ruparelia K, Lydall GJ, Guerrini I et al (2015) Genetic variants in or near ADH1B and ADH1C affect susceptibility to alcohol dependence in a British and Irish population: ADH SNPs protect against ADS. Addict Biol 20(3):594–604
49. Wu C, Kraft P, Zhai K, Chang J, Wang Z, Li Y et al (2012) Genome-wide association analyses of esophageal squamous cell carcinoma in Chinese identify multiple susceptibility loci and gene-environment interactions. Nat Genet 44(10):1090–7
50. Chartier KG, Dick DM, Almasy L, Chan G, Aliev F, Schuckit MA et al (2016) Interactions Between Alcohol Metabolism Genes and Religious Involvement in Association With Maximum Drinks and Alcohol Dependence Symptoms. J Stud Alcohol Drugs 77(3):393–404

Tables

Table 1

Demographic characteristics of alcohol dependent cases and controls
|                          | Cases N=150, n(%) | Controls N=150, n(%) | OR (95% CI)        | P value   |
|--------------------------|------------------|---------------------|-------------------|-----------|
| **Age in years**<sup>a</sup> (mean±SD) | 37.69±0.828      | 33.95±1.096         |                   | 0.0068    |
| **Education**<sup>b</sup> |                  |                     |                   |           |
| Lower (up to high school) | 96(64.0)         | 52(34.7)            | 2.251(1.406-3.604) | 0.001     |
| Higher                   | 54(36.0)         | 98(65.3)            |                   |           |
| **Employment**<sup>b</sup> |                  |                     |                   |           |
| Yes                      | 139(92.7)        | 117(78.0)           | 3.564(1.720-7.464) | 0.0005    |
| No                       | 11(07.3)         | 33(22.0)            |                   |           |
| **Cigarette smoking**<sup>b</sup> |            |                     |                   |           |
| Yes                      | 106(70.7)        | 82(54.7)            | 1.998(1.241-3.217) | 0.0059    |
| No                       | 44(29.3)         | 68(45.3)            |                   |           |
| **Marital status**<sup>b</sup> |              |                     |                   |           |
| Married                  | 112(74.7)        | 78(52.0)            | 2.721(1.670-4.432) | <0.0001   |
| Unmarried                | 38(25.3)         | 72(48.0)            |                   |           |
| **Family history**<sup>b</sup> |              |                     |                   |           |
| Yes                      | 123(82.0)        | 90(60.0)            | 3.046(1.793-5.176) | <0.0001   |
| No                       | 27(18.0)         | 60(40.0)            |                   |           |
| **First use of alcohol, age in years**<sup>c</sup> (mean±SD) | 20.07±5.57       | 20.09±4.16          |                   | 0.8837    |

<sup>a</sup> Student’s t test  
<sup>b</sup> Chi square test  
<sup>c</sup> Pearson correlation test

**Table 2**

Genotype and allele frequencies of *ADH1C* and *ALDH2* among case (n=150) and control (n=150) groups
| SNP  | Gene  | Genotype | Case n(%) | Control n(%) | Allele | Case n(%) | Control n(%) |
|------|-------|----------|-----------|--------------|--------|-----------|--------------|
| rs698| ADH1C | TT       | 57(38)    | 68(45)       | T      | 184(61.3) | 200(66.7)    |
|      |       | TC       | 70(47)    | 64(43)       | C      | 116(38.7) | 100(33.3)    |
|      |       | CC       | 23(15)    | 18(12)       |        |           |              |
| rs671| ALDH2 | GG       | 73(49)    | 93(62)       | G      | 209(69.7) | 236(78.7)    |
|      |       | GA       | 63(42)    | 50(33)       | A      | 91(30.3)  | 64(21.3)     |
|      |       | AA       | 14(09)    | 07(05)       |        |           |              |

**Table 3**

Allelic and genotypic analysis of *ADH1C* and *ALDH2* among case and control groups
| Models               | P value | OR (95% CI)          |
|---------------------|---------|----------------------|
| rs698 (ADH1C)       |         |                      |
| Dominant (TT Vs TC+CC) | 0.2415  | 0.7391 (0.4733 - 1.179) |
| Recessive (CC Vs TT+ TC) | 0.5018  | 1.328 (0.6700 - 2.588) |
| Co-dominant (TC Vs CC+TT) | 0.5615  | 1.176 (0.7433 - 1.867) |
| Additive (CC Vs TT)  | 0.2818  | 1.524 (0.7447 - 3.013) |
| Allelic (C Vs T)     | 0.2020  | 0.7931 (0.5664 - 1.106) |
| rs671 (ALDH2)        |         |                      |
| Dominant (GG Vs GA+AA) | **0.0272**  | 0.5811 (0.3720 - 0.9224) |
| Recessive (AA Vs GG+GA) | 0.1734  | 2.103 (0.8122 - 5.409) |
| Co-dominant (GA Vs GG+AA) | 0.1526  | 1.448 (0.9134 - 2.307) |
| Additive (GG Vs AA)  | 0.0634  | 0.3925 (0.1544 - 0.9832) |
| Allelic (G Vs A)     | **0.0152**  | 0.6228 (0.4328 - 0.9009) |

Pearson's chi-squared test

CI – confidence interval, OR – odds ratio, P value (<0.05) - significant