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THE ROLE OF ALDH2 AND ADH1B POLYMORPHISM IN ALCOHOL DEPENDENCE: A CASE- CONTROL STUDY FROM BILASPUR, CHHATTISGARH, INDIA

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ABSTRACT
Polymorphism at the functional region of the gene encoding Alcohol Dehydrogenase (ADH) 1B and Aldehyde Dehydrogenase (ALDH2) are viewed as most essential among a few hereditary factors causing complex disorder - Alcohol Dependence. From population of India, there is insufficient account of data on commonly studied Arg47His and Glu487Lys polymorphisms from Alcohol Dependent subjects. In this article, we report for the first time, allelic and genotypic frequencies of Arg47His and Glu487Lys single nucleotide polymorphisms (SNPs) in Chhattisgarh population (Central India). A sum of 50 Alcohol Dependent Cases, satisfying DSM IV criteria and 50 age sex matched controls were genotyped utilizing the Polymerase Chain Reaction– Restriction Fragment Length Polymorphism technique. The feature of the examination findings was the interestingly high frequency of the ALDH2*2/*2 genotype (among Alcohol Dependent Cases) being a risk genotype for Alcohol Dependence.

KEYWORDS: Alcohol dependence, alcohol dehydrogenase, aldehyde dehydrogenase, genotype, allele frequency.

INTRODUCTION
Alcohol dependence (AD) is a complex psychiatric condition this is motivated with the aid of both genetic and environmental factors (Stacey et al. 2009). Alcohol Dependence (AD; Mendelian Inheritance in Man, (MIM) %1037800), a persistent relapsing disorder, is a severe health issue globally. It is characterized with the aid of loss of sensitivity and improvement of tolerance to, and withdrawal symptoms and craving for alcohol (Heinz et al. 2004). Alcoholism is a public issue for many nations, as it affects bodily or intellectual fitness, social and familial relationships, and occupational responsibilities (Sun et al, 2002). Alcohol Dependence also leads to a plethora of disabling headaches, which include hepatitis, hepatic cirrhosis, persistent pancreatitis, testicular atrophy and avascular necrosis of the hip joint (Schuckit, 2004). Individuals provide one-of-a-kind responses when exposed to comparable amount of alcohol. Alcoholism ought to be typical as a continual ailment with a complex starting place and final results (Gemma et al. 2006). Livor is the principle organ responsible for alcohol metabolism, the reason at the back of the liver sicknesses based on excessive and prolonged alcoho l intake (Tekin and lter 2005). Alcoholism is an vital purpose of chronic liver sicknesses, but best 10% to 20% of alcoholics increase cirrhosis (Lee et al. 2001) even as a group of drinkers donot develop cirrhosis or other or other persistent liver illness, other companies who in all likelihood devourless alcohol will have full-size liver harm man or woman based genetic versions within the genes encoding the enzymes gambling lively position in ethanol metabolism are considered to be responsible for this distinction (Tekin etal. 2005). Alcohol abuse disordersresult from the interaction between an person's genetic and environmental susceptibility and repeated intake of alcohol over time. It isn't always feasible to grow to be alcoholic without time and again consuming alcohol, best a small percentage of all drinkers emerge as alcoholic (Schramm-Sapyta et al. 2008). It's been demonstrated that among people who drink alcohol, only a minority finally come to be depending on it (Yin et al. 2001). Toxicity of alcohol intake is caused by direct results of ethanol itself through disturbance of cell membrane integrity, enzyme functions and severa metabolic pathways (Harris et. al. 2008).

Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are the foremost enzymes answerable for hepatic metabolism of ethanol (Yin et al. 2001). Aldehyde dehydrogenase (ALDH 2) is one of the primary enzyme engaged in alcohol metabolism. This enxyme occure in numerous paperwork which are

encoded via distinctive genes. The effect of alcohol metabolism on special exclusive body organs is depend on the ethanol awareness and length of publicity of alcohol drinks. Aldehyde dehydrogenase enzyme catalyze the breakdown of acetaldehyde into acetate (Vaswani et al. 2008).

ALDH2*2 in Alcoholism

Acetaldehyde, generated via ethanol oxidation within the liver is further metabolized to acetate by using aldehyde dehydrogenase (ALDH) The high affinity mitochondrial ALDH2 is in particular accountable, but ALDH2 deficiency is commonplace in parts of Asia. The effect of the inactive ALDH2*2 enzyme turned into first investigated by way of Wolfe who found racial differences within the facial flushing reaction throughout alcohol consumptions.

The ALDH2*1 (504Glu) allele encodes an active sub unit even as ALDH2*2(504 Lys) encodes a sub unit that is essentially inactive (therefore causing a build-up of acetaldehyde inside the blood and different tissue) hybridization of an ALDH2*2 enzyme sub unit with an ALDH2*1 sub unit bring about the inactivation of the iso-enzyme and ALDH2 poor phenotype. people homozygous for the ALDH2*2 or heterozygous are therefore deficient in the conversion of acetaldehyde to acetate, have excessive blood acetaldehyde tiers after alcohol consumption and be afflicted by unfavourable response to alcohol, such as facial flushing, nausea, headache and tachycardia, the importance of ALDH2 genetic variation in risk for Alcohol Dependence has been well hooked up among Asian populace where the flushing response is located in fifty seven-80 %of people and the ALDH2*2 allele frequency tiers from 0.25 to 0.35. Heterozygote's are at reduced chance for Alcohol Dependence as compared to ALDH2*1 homozygote's at the same time as people even as individual homozygous for ALDH2*2 have a very low hazard for Alcohol dependence.

ADH1B in Alcoholism

The ADH1B*2 (ADH1B*47His) allele codes for a better pastime enzyme in comparison with the ADH1B*1 (ADH1B*47Arg) allele and is therefore recognised to steer drinking behaviour, ensuing in safety from alcoholism. Chen et al. (1999), in a case control evaluation, found that people having one or two copies of the ADH1B*2 allele and a single copy of ALDH2*2 prone to less hazard (odd ratios 0.04–0.05) for alcoholism, compared with the ADH1B*1/*1 and ALDH2*1/*1 genotype. In addition, the researchers reported that the risk for alcoholism is associated with the ADH1B*2/*2–ALDH2*1/*1 genotype is ready half of that associated with the ADH1B*1/*2–ALDH2*1/*1 genotype. Their result suggests that the protection afforded by using the ADH1B*2 allele may be unbiased of that afforded via ALDH2. A remarkable version in the allele frequency of this polymorphism has been determined among distinctive ethnic groups (Whitfield, 2002). The ADH1B*2 allele is higher in frequency among non-alcoholic than in alcoholic groups in populations from East Asia, Taiwan, Spain, New Zealand and in Jews from Israel and the United States. Because of this very low frequency of the ADH1B*2 allele among the Caucasian population, however, association studies have broadly speaking remained inconclusive (Reddy et al. 2006). Studies of ADH1B*2 allele (Arg47His polymorphism) frequency within the Indian population are inconsistent. Goedde et al. (1992) suggested a 9.9% ADH1B*2 allele frequency in heterogeneous subjects from the Indian populace, whereas some other study from India (at the Kachari populace) reported a frequency of 6.6 percent (Osier et al.2002). Recently, in a robust take a look at related to Indian tribal populations, the polymorphism has been determined to be monomorphic (ADH1B*1/*1), with whole absence of the ADH1B*2 allele (Reddy et al. 2006). Primarily based on their findings, the researchers argued that Indians (especially the ones comprising the lower caste and working class) ought to have advanced tolerance to the detrimental effects of alcohol, and for this reason the safety-conferring ADH1B*2 allele has been selected out from the populace (Vaswani et al. 2008).

Because of the paucity of Indian facts especially from population of Chhattisgarh in regards to ADH1B/ALDH2 gene polymorphisms, the present study is aimed to characterise the Arg47His and Glu487Lys polymorphisms in subjects from Chhattisgarh with AD and to set up the genotype/phenotype correlation (if any).

MATERIALS AND METHODS

In this study, 50 alcohol-dependent male subjects satisfying DSM IV criteria and aged between 18 and 60 years of age, from the OPD of Psychiatry Department of Chhattisgarh Institute of Medical Sciences, Bilaspur (C.G.) and 50 non- alcohol dependents as healthy controls belonging to different ethnic groups and socio-economic background between March- May, 2017 were recruited. Subjects with a history of any other substance abuse/dependence were excluded. In accordance with the Declaration of Helsinki (2000) of the World Medical Association this study was carried out. Ethical committee clearance from the institute was obtained prior to recruitment of subjects. All subjects gave written knowledgeable consent to take part in the study. Information regarding ethnicity, occupation, age at onset of alcohol addiction, frequency of alcohol intake, and any other psychiatric or bodily illness had been assessed and recorded.

Genomic DNA extraction and genotyping

5ml blood sample through vein puncture was collected in a sterile tube containing EDTA-coated vacutainers and stored at 4ºC until processing for DNA extraction was carried out. Genomic DNA was extracted using the standard salting-in salting-out method at Human Genomics Laboratory of School of Studies in

Anthropology, Pt. Ravishankar Shukla University, Raipur (C.G.). Polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP) approach used for SNP genotyping with the help of forward and reverse primer sequences for the amplification of the ALDH2 Glu487Lys were 5'-CAAATTACAGGGT CAAGGGCT-3' (forward) and 5'-CCACACTCACAGTTTTCTCTT-3'(reverse) and respectively; ADH1B Arg47His SNP were 5'-AATCTTTTCTGAATCTGAACAG-3' and 5'-GAAGGGGGGTCACCAGGTTGC-3'. 20 ml of amplified PCR product was divided into two equal portions. For ADH1B, 10 ml of the amplified product was incubated at 37*C for two hours with *NmuCI* and for ALDH2 10 ml was digested with *Mbo II* restriction enzymes (RE). DNA fragments in the RE digested and undigested mixture were analysed on 2.5% Agarose Gel using tris-borate-EDTA (TBE) buffer and observed with the help of known DNA markers. The presence of 95 base pair (bp) and 65 bp restriction fragments indicated the presence of wild-type Arg and mutant His alleles for the ADH1B polymorphism, respectively the presence of 134 bp and 123 bp fragments indicated the presence of wild-type Glu and mutant Lys alleles for the ALDH2 SNP. Genotypes were observed and recorded for further statistical analysis.

Statistical analysis

Comparison of genotypes and allele frequencies between cases and controls with different genotypic profiles for ADH1B and ALDH2 gene polymorphisms were carried out using the MS Excel for allele frequency count and genotype frequency. SPSS 20 is used for calculating the logistic regression and odds ratio for risk of functional polymorphisms of ADH1B and ALDH2 for cases and controls.

RESULTS

The demographic and other alcohol dependent details of the cases and controls are presented in Table 1- 6. A total of 100 cases and controls were recruited into the study. The study group consisted of 50 alcohol dependent cases, aged 18 to 70 years and the control group consisted of 50 non- alcohol dependent men (Table1). Maximum frequencies (24%) were observed for age group between 42-52 years among cases and among controls high frequency (48%) was observed from age group of 18-30 years. Occupation wise distribution of cases and controls reported higher frequency of government servants (36%) in cases and higher frequency of unemployed (32%) among controls (Table2). Category wise distribution of cases and controls were represented in Table 3. OBC was represented in higher frequency (44%) among cases and General reported higher frequency (72%) among controls. Ages of initiation for alcohol intake among cases were higher (48%) in 10-20 years (Table4). The frequency of alcohol intake among cases was higher (52%) on regular basis (Table5) and the type of alcoholic beverage most frequently (56%) consumed by cases were Indian liquors (Table6).

The genotype and allele frequency of cases and controls at ADH1B and ALDH2 were depicted in Table7. The risk genotype ADH1B*1/*1 were higher in cases (56%). The risk allele (ADH1B*1) were also higher (60%) in cases. High frequency (44%) of the ALDH2*1/*2 risk genotype (among alcohol-dependent cases) confer its responsibility of creating alcohol dependency.

Multiple logistic regression analyses revealed that the ALDH2*1/*2 genotype was an dependent variable with strong propensity to develop Alcohol Dependence (AD) (OR 2.90; 95 per cent CI=0.777-4.887; p value=0.012). On comparing, allelic variations of ADH1B exerted no significant effect on the risk of Alcohol Dependence in cases by logistic regression analysis. ADH1B and ALDH2 also showed no significant interaction in the risk for Alcohol Dependence (AD) (Table8).

Table 1. Age Wise Distribution of Cases and Controls.

S. No.	Age group	Case		Control	
		Frequency	%	Frequency	%
1	**18-30**	10	20	24	48
2	**30-42**	10	20	10	20
3	**42-52**	12	24	10	20
4	**52-60**	10	20	4	8
5	**60 Above**	8	16	2	4
Total		**50**	**100**	**50**	**100**

Table 2. Occupation Wise Distribution of Cases and Controls.

S. No.	Occupations	Case		Control	
		Frequency	%	Frequency	%
1	**Government service**	18	36	12	24
2	**Private service**	14	28	6	12
3	**Agriculture**	12	24	4	8
4	**Retired**	2	4	2	4
5	**Businessman**	4	8	10	20
6	**Unemployed**	0	0	16	32
Total		**50**	**100**	**50**	**100**

Table 3. Category wise Distribution of Cases and Controls.

S. No.	Caste	Case		Control	
		Frequency	%	Frequency	%
1	General	8	16	36	72
2	OBC	22	44	14	28
3	SC	6	12	0	0
4	ST	14	28	0	0
Total		50	100	50	100

Table 4. Age of Initiation of Alcohol in Cases.

	Age at initiation	Cases	
S. No.		Frequency	%
1	10 -20	24	48
2	20 -30	22	44
3	30-40	2	4
4	40-50	2	4
Total		50	100

Table 5. Frequency of Intake of Alcohol.

S. No.	Frequency of Intake	Cases	
		Frequency	%
1	Regular	26	52
2	Occasional	6	12
3	Rare	18	36
Total		50	100

Table 6. Distribution of Cases on the Basis of Type of Alcoholic Beverage Consumed by Cases.

S. No.	Type of Liquor	Cases	
		Frequency	%
1	Indian liquor	28	56
2	Foreign liquor	20	40
3	Both	2	4
		50	100

Table 7. Genotype and Allele Distribution of ADH1B and ALDH2 in Cases with Alcohol Dependents and Controls.

Gene	N	Genotype number (frequency)			Allele number (frequency)	
		*1/*1	*1/*2	*2/*2	*1	*2
ADH1B						
Cases	50	28 (0.56)	4 (0.08)	18 (0.36)	0.60	0.40
Controls	50	8 (0.16)	2 (0.04)	40 (0.80)	0.82	0.18
ALDH2						
Cases	50	8 (0.16)	22 (0.44)	20 (0.4)	0.36	0.64
Controls	50	32 (0.64)	8 (0.16)	10 (0.20)	0.52	0.48

Table 8. Risk of functional polymorphisms of ADH1B and ALDH2 for Cases and Controls.

Gene	Regression Coefficient	Standard Error	p-value	Odds Ratio	95% Confidence Interval
ADH1B*1/*2	-0.4196	0.69	0.5428	0.66	0.170-2.539
ADH1B*2/*2	0.2972	0.70	0.6725	0.74	0.187-2.947
ALDH2*1/*2	3.5167	1.32	0.0078	2.90	0.777-4.887
ADH1B × ALDH2	0.7031	0.8658	0.4167		
Constant	1.2854	0.7012	0.0668		

Cases (n = 50); Controls (n = 50). Statistical comparison was evaluated by multiple logistic regression after adjustment.

DISCUSSION

Ethanol metabolism through pharmacokinetics affects the risk for Alcohol Dependence. While the function of ADH1B and ALDH2 genes in predisposition to alcoholism were noticed separately, they have been indicated to act additionally when they both occur. The ADH1B*2 and ALDH2*2 alleles increase the levels of acetaldehyde by raising the amount of manufacturing and lessening the rate of metabolism correspondingly, thus accompanying but not in cooperative manner (Vaswani et al. 2008).

The present study revealed a significant difference in ALDH2 genotypes between the cases and control groups. The allele frequencies of ALDH2*2 were lower in the cases than in the control group.

By alteration at two different sites of the genomic level, the allelic series for ADH1B is generated at the protein level. The allele ADH1B*1 is comprised of 47Arg and 369Arg; the allele ADH1B*2 is comprised of 47His and 369Arg; and the ADH1B*3 allele is comprised of 47Arg and 369Cys. Goedde et al. (1992) reported largely monomorphic frequency for the ADH1B*1 allele among Caucasians, with a extremely low frequency of the ALDH2*2 allele. Osier et al. (2002) revealed that the ADH1B*2 allele, for confering protection against alchol dependence which is fairly common in East Asian populations. This allele was found to be present at considerable frequency; 0.60 in cases and 0.82 in controls. Our finding do not corresponds with the observations by Reddy et al. (2006) in tribal populations from southern India and Vaswani et al (2008) in patients North Indian population.

The extremely low frequency of the ADH1B*2 allele in tribal populations of south India was reported by Reddy et al. (2006). Vaswani et al. (2008) also observed such low frequencies in their study. Ou findings are not consistent with their findings but shows correspondence with the moderate frequencies observed for neighbouring East Asian population and response towards protection against alcoholism (Osier et al. 2002). Such moderate frequency of ADH1B*2 in cases and controls in the present study could indicates that no selection pressure is effective against the ADH1B*2 allele in population of Chhattisgarh entitled its ability to protect the Indian population from Alcohol Dependency (AD). On chromosome 12q24, the gene ALDH2 is located. A difference of single bp (G to A; Glu487Lys) at exon 12 triggers the ALDH2*1 normal allele, to turn out to be a non-functional (ALDH2*2) allele, coding inactive enzyme (Yoshida et al. 1996).

Wall et al. (2003) reported prevalence of ALDH2*2 allele, in Asian populations but is very rare among non-Asians and provides strongest protection for AD. Subjects from Asia are homozygous for ALDH2*2 and are more or less likely of developing AD, however heterozygotes (ALDH2*1/2*2) genotypes are about one-third times risk of alcohol dependence as compared to those devoid of this allele. Assanangkornchai et al. (2003) observed a very low frequency (0–0.3%) of homozygous ALDH2*2/*2 genotype among alcoholic patients, while the nonalcoholic subjects were observed with 3–12% having this genotype. ALDH2*1/*2 heterozygous genotype was observed with frequency of 6–17% of alcohol-dependent cases as compared to non-alcoholic controls with 30–45% (Thomasson et al. 1993; Chao et al. 1994; Higuchi et al. 1996). Our obervation are consistent with the above findings and implies that the functional polymorphism at the gene encoding ALDH enzyme influences the susceptibility to develop Alcohol Dependence (AD). The furthermost significant observation of the present study was the high frequency of the ALDH2*1/*2 genotype among AD cases indicating a risk genotype for AD.

Therefore, on the basis of these findings based on a limited sample size, it could be postulated that the Chhattisgarh population genotype is susceptible to gradual metabolism of alcohol and fast metabolism of acetaldehyde and thus predisposed to alcoholism. Observations made in the present study should be looked with the assessment of the conceivable inadequacy impersonated by the lack of data on from various population of India. Further, on larger sample size and in depth investigations on the role of candidate gene polymorphisms regarding understanding the genetics of Alcohol dependence from other biochemical pathways needs to be focused.

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