Assessment of ADH1B, ALDH2, GSTM1 and GSTT1 Gene Polymorphic Frequencies among Alcoholics and Controls in the Arcadian Population of Central India

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Abstract

**Background:** Epidemiological research has highlighted the global burden of primary liver cancer cases due to alcohol consumption, even in a low consumption country like India. Alcohol detoxification is governed by ADH1B, ALDH2, GSTM1 and GSTT1 genes that encode functional enzymes which are coordinated with each other to remove highly toxic metabolites i.e. acetaldehyde as well as reactive oxygen species generated through detoxification processes. Some communities in the population appears to be at greater risk for development of the liver cancer due to genetic predispositions.

**Methods:** The aim of this study was to screen the arcadian population of central India in order to investigate and compare the genotype distribution and allele frequencies of alcohol metabolizing genes (ADH1B, ALDH2, GSTM1 and GSTT1) in both alcoholic (N=121) and control (N=145) healthy subjects. The gene polymorphism analysis was conducted using PCR and RFLP methods. **Results:** The allele frequency of ALDH2 *1 was 0.79 and of ALDH2*2 was 0.21 (OR:1.12; CI (95%): 0.74-1.71). The null allele frequency for GSTM1 was 0.28 (OR:0.85; CI (95%): 0.50-1.46) and for GSTT1 was 0.20 (OR:1.93; CI (95%): 1.05-3.55). No gene polymorphism for ADH1B was not observed. The total prevalence of polymorphisms was 3.38% for ALDH2, GSTM1 and GSTT1.

**Conclusion:** The results of this study suggested that individuals of the Central India population under study are at risk for liver disorders due to ALDH2, GSTM1 and GSTT1 gene polymorphisms. This results may have significance for prevention of alcohol dependence, alcoholic liver disorders and the likelihood of liver cancer.

**Keywords:** Alcoholic- xenobiotic machinery- gene polymorphism- reactive oxygen species

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which are mainly alcohol dehydrogenase (ADH1B), aldehyde dehydrogenase (ALDH2) and cytochrome P-450 enzymes while phase II enzyme, glutathione-S-transferase (GSTM Mu1 and GST Teta1) family conjugate ROS to less reactive and water soluble products. These enzymes assist sudden withdrawal of alcohol molecules, making it possible to eliminate it from the body and reduces the risk of ALD and liver cancer (Gubergrits et al., 2014; Mansoori and Jain, 2015) (Figure 1A and 1B).

After consumption, alcohol is converted into acetaldehyde (ACH) in hepatocytes, catalyzed by ADH1B enzyme. ACH is highly toxic molecule that trigger ROS production. ACH is further metabolized by ALDH2 into less reactive byproduct acetate, which is broken down into water and carbon dioxide for easy elimination from the body. Most of the acetate takes part in other metabolic pathways like Kreb’s cycle in mitochondria for production of energy (Zakhari, 2013). The conjugation of reduced glutathione is catalyzed by GSTs enzymes in phase II thereby reducing the reactivity of the intermediate compounds by making them water soluble and assist their elimination from the body (Ali et al., 2015).

ADH1B gene positioned at 4q23 chromosome and possess three different ADH1B alleles (ADH1B*1, ADH1B*2 and ADH1B*3). The ADH1B polymorphism occurs due to Arg→His transition (also named Arg487His, with the arginine corresponding to ADH1B*1 allele, and histidine corresponding to ADH1B*2 allele). The substitution resulted encode enzymes that have a 70 to 80 fold higher turnover rate than β1 subunit because the coenzyme is released more rapidly at the end of the reaction. If the subject carries two copies of the allele ADH1B*1 (Homozygous for ADH1B*1), account for approximately 70 percent of the liver’s total ethanol oxidizing capacity, except for those subjects having ADH1B*2 variant allele (Liu et al., 2016).

ALDH2 located on chromosomes 12q24.2 is an essential enzyme for ACH elimination, and its polymorphism regulate blood ACH concentrations after alcohol consumption. Polymorphism occurs in ALDH2 gene due to Glu→Lys transition (also named Glu487Lys, with the glutamate corresponding to ALDH2*1 allele, and lysine corresponding to ALDH2*2 allele). ALDH2*2 allele is highly prevalent among the East Asian population (He et al., 2016). ALDH2*2 allele encodes an enzyme that results in low enzymatic activity. ALDH2*2 (homozygotes and heterozygotes) have higher ACH levels in the blood than in ALDH2*1 (homozygotes). The high level of ACH in the blood (i.e. through ALDH2 polymorphism) is considered the risk and susceptibility to ALD and liver cancer (Liu et al., 2016).

GSTM1 and GSTT1 genes are positioned at chromosome locus 1p13 and 22q11 respectively. Both genes encode for functional enzymes that are responsible for the conjugation or transfer of the glutathione group to the reactive intermediates i.e. ROS that are generated during alcohol metabolism. Conjugation transform highly reactive molecules into a less reactive form and help liver cells to maintain the ROS level that protects from oxidative stress and confer shield against a wide variety of toxic insults (Yamada et al., 2014; Gorukmez et al., 2016).

Activities of GSTM1 and GSTT1 enzyme are different in different human cohorts due to hereditary differences resulted due to genetic polymorphisms or null genotype (Broekman et al., 2014). When an individual lacks GSTM1 and/or GSTT1 genes, then in this situation cell lack functional enzyme that acts on ROS and therefore the level of ROS enhances. The null genotype of GSTM1 and GSTT1 have been linked to the dysfunction of respective genes, that influence the alcohol metabolism. Since the polymorphism of these metabolizing genes influence the detoxifying action, they have been suggested to play an important role in ALD, cancer susceptibility and prognosis (Koh et al., 2011; Malik et al., 2016).

A population of central India (district Sagar and Damoh of state Madhya Pradesh, India) was selected for this study because the larger portion consists of rural and tribal people. They are less educated and unaware about the ill-effects of alcohol consumption due to very low socioeconomic status. Generally males of this population are predominantly engage in chronic alcohol consumption and addicted to it. Rural area lacking medical surveillance and facilities for the detection of ALD, therefore resulted into unnoticed morbidity and mortality due to progression towards liver cancer. Thus the present study carried out in order to investigate and compare genotype and allele frequencies of alcohol metabolizing genes (ADH1B, ALDH2, GSTM1 and GSTT1) in both alcoholic and non-alcoholic healthy subjects and to evaluate the polymorphisms susceptibility to alcohol-induced liver disorders including liver carcinoma. There is no gene polymorphism data exist that define the cancer risk susceptibility for the population under study.

Materials and Methods

Subject selection and blood sample collection

Normal healthy 266 male individuals were selected for this study, out of which 145 individuals as control who neither consume alcohol nor smoke and 121 individuals were alcoholic with no evidence and symptoms of liver disorders as enquired by a medical officer and on the basis of information collected from individuals and their family members. About 56 alcohol users were having smoking habit too. Subject information about age, sex, diet, alcohol intake (dose as well as time), smoking habit and medical history of the family was obtained through written preinformed consent form prior to blood collection from the individuals (Table 1). Recruited subjects belong to those villages of Sagar and Damoh district of Madhya Pradesh which are parts of central India where people are known to consume country liquor on regular basis depending upon the filled up questionnaire people excluded who do not consume alcohol. The blood sample was drawn by venipuncture from each subject in 5ml sterile EDTA coated vials (Labtech K3EDTA). Collected blood samples were stored at 4 °C during transportation and finally transferred to -20 °C for future use.

DNA Extraction and genotyping for polymorphism analysis

Genomic DNA was isolated from lymphocytes by
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Using Wizard Genomic DNA purification kit (Promega A1120) method. After extraction, quality of DNA was assured by 0.8% Agarose gel (AG) electrophoresis and quantification was done by evaluating absorbance (A260/A280) through UV Spectrophotometer (2100/2100 Cole-Parmer Ins. Company, USA). DNA samples were stored at -20°C. Isolated genomic DNA (10-100ng) was amplified through polymerase chain reaction (PCR) in a total volume of 25µl reaction mixture containing 1X Kapa HiFi Hotstart Ready Mix (that contains 0.5U DNA Polymerase, 0.3mM dNTPs each, 2.5mM MgCl₂) (Cat.No. KK2601), with specific forward primer and reverse primer 10pmol each (Table 2) and nuclease free water was used for final volume makeup for all reactions. After PCR, amplicons size with the help of 100bp DNA ladder (NEB,US) were analyzed by gel electrophoresis using ethidium bromide (EtBr) stained (10mg/ml) 2% AG (Sigma).

ADH1B Genotyping
ADH1B polymorphism was analyzed by restriction fragment length polymorphisms (RFLP) method described by Konishi et al., (2004). The PCR cycling condition for reaction mixture was initial denaturation at 95°C for 3 mints, followed by 35 cycles of denaturation at 98°C for 20 secs, annealing at 57°C for 20 secs and extension at 72°C for 35 secs. The ADH1B PCR product 155bp was digested with MaeIII (Cat.No. Sigma 10822248001) and the presence of the ADH1B*2 allele yielded two fragments of 95bp and 60bp while the *1 allele produced a single uncut fragment of 155bp on an EtBr stained 2.0% AG. The amplicon of 119bp was visualized on 1.8% AG by electrophoresis. The PCR products were then digested with Eco RI (Cat. No.NEB-R0529S) and yield fragments of 90bp and 18bp in the presence of the ALDH *I allele or the single uncut 108bp fragment in the presence of the ALDH*2 allele on an EtBr stained 2.0% AG. The wild and variant genotypes were determined by the band pattern obtained.

Statistical Analysis
The distribution of the genotype frequency of ADH1B, ALDH2, GSTM1 and GSTT1 gene was determined. Using the χ² test, the Hardy-Weinberg equilibrium for the gene polymorphism in alcoholics and controls was analysed. Odd ratio (OR) and relative risk (RR) with 95% Confidence Interval (CI) and P value was analyzed for the same using SPSS software. Levels of significance for all statistical analyses were set at P <0.05.

Results
In order to evaluate genotype and allelic frequency of ADH1B, ALDH2, GSTM1 and GSTT1 gene, the PCR tool was used for the diagnosis of gene polymorphism. After PCR amplification of isolated genomic DNA with specific primers, observations as per Figure 2, 3, 4 and 5 of 2% AG was done. In ADH1B analysis (Figure 2), no digested bands of 95bp and 60bp were obtained, confirmed the absence of a mutant variant allele of ADH1B gene. But in ALDH2 (Figure 3), variant allele were obtained. In Lane 7, single uncut band of 119bp represent the homozygous wild allele *1/*1 (Glu/Glu), Lane 3-6 showed one uncut (119bp) with two digested fragments (90bp and 18bp) represent the heterozygous allele *1/*2 (Glu/Lys) and Lane 1-2 showed two digested fragments of 90bp and

Figure 1. A, Xenobiotic pathway for alcohol detoxification includes two phases, phase I: Oxidative pathway and phase II: Non-oxidative pathway; B, Consequences due to Gene polymorphism (if present in any one of the genes) in ADH1B, ALDH2, GSTM1 and GSTT1 genes, that increase ROS level, results in to DNA Damage that cause alcoholic liver disorders and finally liver carcinoma (Mansoori and Jain, 2015).

Figure 2. For ADH1B Genotyping—Lane L, 100bp DNA Ladder, Lane 1–7, Undigested 155bp bands for ADH1B.
18bp bands which represents the homozygous mutant allele *2/*2 (Lys/Lys). The absence of 215bp and 480bp indicate null genotype for GSTM1 and GSTT1 gene that was obtained in Figure 4 and 5, respectively.

In the study gene polymorphism associated with ADH1B was not found. Table 3 represents the distribution of genotype frequency of alcohol metabolizing genes (ALDH2, GSTM1 and GSTT1) in control and alcoholic subjects. Among the 266 subjects recruited, the distribution of genotype frequency of ALDH2 for homozygous wild allele *1/*1 (Glu/Glu) was 161 (60.53%), heterozygous variant allele *1/*2 (Glu/Lys) was 97 (36.47%) and homozygous mutant allele *2/*2 (Lys/Lys) was 8 (3.01%). The mutant type allele *2/*2, associated with alcoholic subjects only was observed and were much lesser. Out of 266, the genotype frequency 75 (28.20%) was found to be digested fragments of 90bp and 18bp bands; Lane 3–6, One uncut (119bp) with two digested fragments (90bp and 18bp); Lane 7, Undigested band (119bp).

**Figure 3.** For ALDH2 Genotyping–Lane L, 100bp DNA Ladder; Lane 1–2, Digested fragments of 90bp and 18bp bands; Lane 3–6, One uncut (119bp) with two digested fragments (90bp and 18bp); Lane 7, Undigested band (119bp).

**Figure 4.** GSTM1 Genotyping; Lane L, 100bp DNA Ladder; Lane 1, Null allele for GSTM1; Lane 2–6, Positive allele for GSTM1 (215bp).

| Variables | Control | Alcoholic |
|-----------|---------|-----------|
| Subjects (N=266) | 145 | 121 |
| Gender | Only males were considered | |
| Age range (year) | 20-70 | 20-70 |
| (Mean + SD) | (35 + 10.34) | (36 + 12.82) |
| Weight range (Kg) | 49-75 | 49-90 |
| (Mean + SD) | (63.8+10.01) | (67.1+13.9) |
| Body Mass Index (Kg/m²) | 20.72 + 2.5 | 24.23 + 3.2 |
| Vegetarian | 79 | 70 |
| Non Vegetarian | 66 | 51 |
| Smokers/ Non-smoker | 0/145 | 56/65 |

**Table 1. Demographic Details of the Population Under Study**

**Table 2. List of PCR Primers Sequence Used for Gene Polymorphism Study**

- **ADH1B**
  - Forward: 5’-AATCTTTTCTGAATCTGAACAG-3’
  - Reverse: 5’-GAAGGGGGGTCAACCAGGTGG-3’

- **ALDH2**
  - Forward: 5’-GTTTGGAGCCCAGTAACCCTT-3’
  - Reverse: 5’-CCCACACTCACAGTTTTGAATT-3’

- **GSTM1**
  - Forward: 5’-AACTCCCTGAAAAGCTAAAGC-3’
  - Reverse: 5’-GTTGGGCTCAAATATACGGTGG-3’

- **GSTT1**
  - Forward: 5’-TTCTTACTGTCCTTCACATCTC-3’
  - Reverse: 5’-TCACGGGATCATGGCCAGCA-3’

**Table 3. Distribution of Genotype and Allelic Frequency of Alcohol Metabolizing Genes (ALDH2, GSTM1 and GSTT1) in Controls and Alcoholics (n=266)**

| Gene | Control (n=145) | Alcoholic (n=121) | Genotype Percentage | Allelic frequency | Odd Ratio(OR) |
|------|-----------------|-------------------|--------------------|------------------|---------------|
| ALDH2 | *1/*1 (Glu/Glu) | 86 (59.31%) | 75 (61.98%) | 161 (60.53%) | *1 (p) =0.79 |
| | *1/*2 (Glu/Lys) | 59 (40.69%) | 38 (31.40%) | 97 (36.47%) | *2 (q) = 0.21 |
| | *2/*2 (Lys/Lys) | 0 | 8 (6.61%) | 8 (3.01%) | \( \chi^2 = 2.15 \) |
| GSTM1 | Positive | 102 (70.34%) | 89 (73.55%) | 191 (71.80%) | 0.72 |
| | Null | 43 (29.66%) | 32 (26.45%) | 75 (28.20%) | 0.28 |
| GSTT1 | Positive | 123 (84.83%) | 90 (74.38%) | 213 (80.08%) | 0.8 |
| | Null | 22 (15.17%) | 31 (25.62%) | 53 (19.92%) | 0.2 |
have a GSTM1 null (homozygous deletion for GSTM1) while the remaining 191 (71.80%) individuals were positive for GSTM1 (had at least one functional GSTM1 allele). 53 (19.92%) were found to have a GSTT1-null genotype; the remaining 213 (80.08%) individuals were positive for GSTT1. The GSTM1 null genotype was slightly higher in control (29.66%) than alcoholic (26.45%), but the GSTTI null genotype was higher in alcoholic (25.62%) than control (15.17%). The null genotype frequency of GSTM1 (28.20%) was higher than GSTT1 (19.92%) when compared.

The observed allele frequency of ALDH2 for *1 (Glu) was 0.79 and *2 (Lys) was 0.21, this genotype distribution which follows the Hardy Weinberg equilibrium and the odds ratio was OR: 1.12; CI (95%) 0.74 - 1.71 (Table 3). The allele frequency for GSTM1 for null and positive was 0.28 and 0.72, respectively and the odds ratio was OR: 0.85; CI (95%): 0.50-1.46. Likewise, there was a slight difference in allele frequency for GSTT1 for null and positive was 0.20 and 0.80, respectively and the odds ratio was OR: 1.93; CI (95%): 1.05-3.55. By observing gene polymorphism frequency of all genes, the maximum risk of dysfunction of xenobiotic machinery is due to GSTM1 gene, then GSTTI in an array. The combined gene polymorphism was 3.38% observed in the individuals exhibited polymorphism in all the genes i.e. ALDH2 (Heterozygous and homozygous mutant), GSTM1 and GSTT1 (null genotype for both) (Table 4). About 28.19% of individuals exhibits both GSTM1 and GSTT1 null genotype and are at higher risk due to gene dysfunction.

Discussion

During ethanol consumption, different xenobiotic genes encoding the alcohol metabolizing enzymes are coordinated with each other and accompanied the removal of the highly toxic metabolite ACH as well as ROS generated by them. In brief, the concentration of ethanol and acetaldehyde in blood is dependent on the relative reaction rate of two major catalyzing enzymes in the liver ADH1B and ALDH2 during xenobiotic detoxification (Wang et al., 2016). While the GSTM1 and GSTT1 act as a cellular guard against ROS after the glutathione conjugation. The glutathione S-transferases are genotypically and phenotypically polymorphic with variable genotype frequencies in different ethnic groups confers difference in ROS detoxification rate in different ethnic groups (Jain et al., 2006; Mansoori and Jain, 2015).

In this study the genotype and allelic frequency of ADH1B, ALDH2, GSTM1 and GSTT1 gene have been analysed in the arcadian population of central India. Population admixture is an important concern, particularly in countries like India, having a genetically heterogeneous population. In order to avoid that problem, independent random control individuals were genotyped along with alcoholics. The ADH1B*1 was the most common type of genotype with no ADH1B*2 variant type alleles in the recruited individuals. This finding suggest that there is no gene polymorphism related to ADH1B gene found in the population under this study and the results show the protective effect of ADH1B against alcohol consumption i.e. convert alcohol into acetaldehyde efficiently and thus increase alcohol tolerance (Matsuo et al., 2007, Malhotra et al. 2016).

In ALDH2 gene, ALDH2*1 allele encode functional enzyme subunit. The ALDH2*2 variant genotype frequency was approximately 40% (both heterozygous (36.47%) and homozygous (3.01%) variants). The heterozygous ALDH2*2 genotype frequency was significantly higher in control than alcoholic individuals, but the homozygous ALDH2*2 genotype frequency was only present in alcoholics. Alcoholics with homozygous variants and heterozygous variants of both control and alcoholic are at high risk of advanced alcoholic liver disease due to accumulation of acetaldehyde. Many studies revealed that ALDH2*2 allele affects drinking behavior and reduced alcohol consumption among the individuals who carry one or two ALDH2*2 alleles. ALDH2*2 may contribute to susceptibility to alcohol dependence and serves as a strong protective factor against alcoholism by making drinking unpleasant (Liu et al., 2016). This population prevailed ALDH1B*1 (60.53%) allele as a higher genotype frequency that are alcohol tolerance in nature. Acetaldehyde metabolic impairment results from insufficient functions of ethanol metabolism enzymes and this case can make a contribution to alcohol abuse and alcoholism (Ding et al., 2009). Various genetic studies concluded that there are different genotype and allele frequency of ADH1B and ALDH2 gene in different racial or ethnic population of the globe (Chinnaswamy et al.,...
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This study, null genotype frequency of GSTM1 and GSTT1 were of high significance. The finding suggests that the GSTM1 null genotype frequency (28.20%) is more common in this population, which is higher when compared with the GSTT1 null genotype frequency (19.92%). Control (29.66%) and alcoholic (25.62%) individuals are at higher risk due to GSTM1 and GSTT1, respectively. Comparison of the null polymorphism frequency of GSTM1 and GSTT1 in South Indian population was done by Vetriselvi et al. (2006). They found that the GSTM1 and GSTT1 null genotype frequencies were found to be 22.4% and 17.6% respectively (Sharma et al., 2012). The frequency of GSTM1 null alleles display race and ethnic variations, being higher in Europeans (42–60%) and Asians (41–63%) compared with that of Africans (16–36%). However, the frequency of GSTT1 null genotypes is somewhat less in Europeans (13.31%) compared with that of Africans (14–57%) and in Asians (35–48%) (Kasthurinaidu et al., 2015).

The null polymorphism of GSTM1 and GSTT1 causes impairment of ROS conjugation of phase II in xenobiotic machinery. This further imbalance the ROS elimination process and cause oxidative insult because of elevated ROS level. ROS interferes with the body’s normal defense mechanism against the toxic intermediates through numerous processes, particularly in the liver (Koh et al., 2011). Moreno and Reyes (2014) reviewed that ROS production and oxidative stress in liver cells play a central role in the development of alcoholic liver disorders. Gene polymorphism results in dysfunction of various genes involved in detoxification of alcohol and other toxic compounds (nicotine and various drugs), consequences in generating various types of alcoholic liver disorders (Koh et al., 2011). Individuals having a null genotype or allele variants and/or carriers of at least one gene for ADH1B, ALDH2, GSTM1 and GSTT1 allele were considered at high risk for alcoholic liver disorders and liver cancer progression (Mendez et al., 2010; Heit et al., 2015).

Gene polymorphism associated with ADH1B, ALDH2, GSTM1 and GSTT1 genes drove much attention in recent years because genetic polymorphism proposed as being the major cause of inter-individual differences in xenobiotic metabolism. Our results suggested that individuals of the population are at ALD risk due to gene polymorphism and exacerbated pressure for the progression of liver cancer. This study is important for social welfare of people and a crucial step to make people aware about the harmful effects of alcohol and prevention against development of alcohol dependence, ALD and cancers. Subsequently, this information could be useful in assessing the genetic risk factors to liver cancer susceptibility and other disorders associated with detoxification pathway. Thus, it is recommended that a larger population should be screened in order to confirm the results of the present study and to relate these data to the geographical difference in disorders associated with the ADH1B, ALDH2, GSTM1 and GSTT1 gene polymorphisms in India. The population under study has low socio-economic status therefore individuals of this population are more prevailed to consume country liquor. Thus just by observing gene polymorphism in an individual’s blood sample the person may be warned of future health risk. This study decipher that liver cancer is the major cause of high mortality among rural population of central India due to genetic predisposition of candidate genes that enhances ROS level and accountable for various liver disorders from chronic alcohol consumption.

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