RESEARCH COMMUNICATION

# Alcohol dehydrogenase 1B and Aldehyde dehydrogenase 2 Polymorphisms in Uzbekistan

**Keun Soo Ahn[1], Shavkat Abdiev[1], Bakhodir Rahimov[1], Yusuf Malikov[1], Saidkarim Bahramov[1], Rieko Okada[2], Mariko Naito[2], Nobuyuki Hamajima[2]***

## Abstract

**The alcohol dehydrogenase 1B (ADH1B) *2 (47His) allele and the aldehyde dehydrogenase 2 (ALDH2) *2 (487Lys) allele are seen among some Asian peoples, but rare among other ethnic groups. This study examined the allele frequencies in the Uzbekistan Republic, which is located in Central Asia. Subjects were derived from a case-control study on peptic ulcer disease, which included 161 Uzbeks and 23 Russians. They were enrolled at the Republic Research Center of Emergency Medicine located in the capital, Tashkent City. Genotyping was performed for ADH1B Arg47His and ALDH2 Glu487Lys with a polymerase chain reaction with confronting two-pair primers. The frequency for the ADH1B *2 allele was similar among cases and controls. The ALDH2 *2 allele was rare in both. Among 161 Uzbeks, the ADH1B *2 allele frequency was 0.286 (95% confidence interval, 0.237-0.338) and for the ALDH2 *2 allele was 0.016 (0.005-0.036), while among the 23 Russians the figures were 0.083 (0.024-0.208) and 0.000 (0.000-0.077), respectively. There were no significant differences in drinking habits among individuals with different genotypes, although ALDH2 *2*2 genotype was not observed. The present study demonstrated that ADH1B *2 allele frequency among Uzbeks was closer to that among Caucasians than East Asians, some Uzbeks also demonstrating the ALDH2 *2 allele.**

**Key Words:** *ADH1B - ALDH2* – polymorphism - Uzbekistan - Uzbeks/Russians

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## Introduction

It is well known that enzyme activities of alcohol dehydrogenase 1B (ADH1B) and aldehyde dehydrogenase 2 (ALDH2) are determined mainly by the genotypes of ADH1B Arg47His in chromosome 4q22 and ALDH2 Glu487Lys in chromosome 12q24.2, respectively (Bosron and Li, 1986). ADH1B *2 (His) allele has a higher enzyme activity to convert ethanol to acetaldehyde, which causes uncomfortable symptoms, resulting in the risk reduction of alcoholism (Borras et al., 2000). ALDH2 *2 (Lys) allele has a very low enzyme activity, resulting that those with ALDH2 *2*2 genotype generally do not become drinkers because of strongly reduced ability to detoxify acetaldehyde. To date, five polymorphisms (G-539T, C-530T, G-357A, -346G Ins/Del, and CG-204GC) of ALDH2 promoter region have been reported other than Glu487Lys, but their functional modification is negligible (Harada et al., 1999).

The enzyme activities of ADH1B and ALDH2 influence the incidence of alcohol related diseases including cancers (Yokoyama et al., 2002; Brennan et al., 2003), liver cirrhosis (Yamouchi et al., 1995) and alcoholism (Edenberg 2007). The effect of nitroglycerin was recently reported to be weaker among those with ALDH2 *2 allele(s), because the drug is activated with ALDH2 (Li et al., 2006). It was also reported that those with ALDH2 *2 allele had a high risk of Alzheimer's disease (Ohta and Ohsawa, 2006).

The allele frequencies of both polymorphisms vary largely among different ethnic groups. The ALDH2 *2 allele is not common except in Chinese, Koreans, and Japanese. Genetic analysis found that these three groups make a cluster (Kim et al., 2005). The ADH1B *1 allele is prevalent among Caucasians and Africans, but not among Asians (Chen et al., 1994; Goedde et al., 1992; Oota et al., 2004). Although the allele frequencies have been reported for most of ethnic groups, the reports for persons in the Central Asia are still limited. This study reports the allele frequencies among those in Uzbekistan Republic, which has a long history of interactions between Asia and Europe including the ancient expansions of nomadic tribes to the west and the establishment of Mongol Empire of the 13th century (Zerjal et al., 2002).

## Materials and Methods

Subjects were derived from a case-control study on

*[1]Republican Research Center of Emergency Medicine of Uzbekistan Republic Ministry of Health, Tashkent, Uzbekistan Republic, [2]Department of Preventive Medicine / Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Nagoya, 466-8550 Japan, *For Correspondence: nhamajim@med.nagoya-u.ac.jp*

the association between *Helicobacter pylori* infection and peptic ulcer disease (PUD) in Uzbekistan Republic (Abdiev et al., 2008). There were 197 participants (103 males and 94 females) enrolled from January to March of 2007 at Republic Research Center of Emergency Medicine (RRCEM) in Tashkent; 60 volunteers of students/staff of the Center, 95 patients with PUD (85 duodenal ulcer patients and 10 gastric ulcer patients), and 42 patients with miscellaneous diseases including 17 with acute cholecystitis, 14 with acute appendicitis, 4 with hernia, 3 with pancreatitis, 2 with echinococcus infection, 1 with nephritis, and 1 with pneumonia.

The subjects were 161 Uzbeks, 23 Russians, 4 Koreans, and 7 others (4 Kazaks, 1 Tatar, 1 Armenian, and 1 Afghan). The analysis was conducted mainly for Uzbeks and Russians. Information on age, sex, ethnicity, and alcohol habits were obtained from medical records (patients) and questionnaire/interview (healthy volunteers). Concerning ethnicity, that in their passport was used. The question on alcohol drinking was simple and subjective; "Are you an alcohol drinker?". Written informed consent was obtained from each participant before blood draw. The study was approved by Ethics Committee of Nagoya University School of Medicine (approval number 459). Genotyping was performed after the complete anonymization of samples.

From each enrolled person 7.5 ml of venous blood was taken. DNA was extracted from 2.5 ml of heparinized blood. ADH1B Arg47His and ALDH2 Glu487Lys were genotyped with a polymerase chain reaction with confronting two-pair primers (PCR-CTPP) (Tamakoshi et al., 2003). The statistical analysis was conducted with STATA version 7.0 (STATA Corporation Inc., College Station, TX). The 95% confidence intervals (CI) of the percentages were calculated based on binomial distributions. Chi-square tests and Fisher's exact tests were performed to examine the differences in percentage.

## Results

DNA was not extracted from two Uzbek patients with PUD. The frequency for ADH1B *2 allele was similar among 56 healthy volunteers (49 Uzbeks and 7 Russians), 90 patients with PUD (78 Uzbeks and 12 Russians), and the other 38 patients (34 Uzbeks and 4 Russians); 0.286, 0.314, and 0.221 for Uzbeks and 0.071, 0.083 and 0.125 for Russians, respectively. ALDH2 *2 allele was rare; 4 out of 156 alleles of Uzbek PUD patients, and 1 out of 68 alleles of Uzbek patients with the other diseases. Since the genotype frequencies were not related to the diseases, the further analyses were conducted for all the subjects combined. The genotype frequencies in total were in Hardy-Weinberg equilibrium (p=0.343 for ADH1B and p=0.852 for ALDH2). Table 1 shows the frequencies according to ethnic group. Among 161 Uzbeks, ADH1B *2 allele was 0.286 (95% confidence interval, 0.237-0.338) and ALDH2 *2 allele 0.016 (0.005-0.036), while among 23 Russians 0.083 (0.024-0.208) and 0.000 (0.000-0.077), respectively. The difference in the ADH1B *2 allele frequency between Uzbeks and Russians was statistically significant (p=0.004 for Fisher's exact test).

**Table 1. Genotype/allele Frequencies according to Ethnic Group**

| Genotype | 161 Uzbeks | | 23 Russians | | 4 Koreans | | 7 others | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| ADH1B Arg47His | | | | | | | | |
| ArgArg | 84 | 52.2 | 19 | 82.6 | 1 | 25.0 | 4 | 57.1 |
| ArgHis | 62 | 38.5 | 4 | 17.4 | 1 | 25.0 | 3 | 42.9 |
| HisHis | 15 | 9.3 | 0 | 0.0 | 2 | 50.0 | 0 | 0.0 |
| Arg allele | 230 | 71.4 | 42 | 91.3 | 3 | 37.5 | 11 | 78.6 |
| His allele | 92 | 28.6 | 4 | 8.7 | 5 | 62.5 | 3 | 21.4 |
| ALDH2 Glu487Lys | | | | | | | | |
| GluGlu | 156 | 96.9 | 23 | 100.0 | 2 | 50.0 | 7 | 100 |
| GluLys | 5 | 3.1 | 0 | 0.0 | 2 | 50.0 | 0 | 0.0 |
| LysLys | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Glu allele | 317 | 98.4 | 46 | 100 | 6 | 75.0 | 14 | 100 |
| Lys allele | 5 | 1.6 | 0 | 0.0 | 2 | 25.0 | 0 | 0.0 |

**Table 2. Genotype and Alcohol Intake Habit according to Genotype**

| Genotype | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | T | Drinkers* | P-value | T | Drinkers* | P-value |
| ADH1B Arg47His | | | | | | |
| ArgArg | 56 | 42 (75.0) | 0.178 | 52 | 7 (13.5) | 0.733 |
| ArgHis | 34 | 22 (64.7) | | 36 | 7 (19.4) | |
| HisHis | 12 | 11 (91.7) | | 5 | 1 (20.0) | |
| ALDH2 Glu487Lys | | | | | | |
| GluGlu | 97 | 71 (73.2) | 0.737 | 91 | 15 (16.5) | 0.531 |
| GluLys | 5 | 4 (80.0) | | 2 | 0 (0.0) | |
| LysLys | 0 | 0 (0.0) | | 0 | 0 (0.0) | |
| Total | 102 | 75 (73.5) | | 93 | 15 (16.1) | |

T, total; *number (%); p values were calculated from 2 by 3 chi-square tests

Table 2 shows the drinker percentages according to sex and genotype. There were no significant differences in drinker percentage among three ADH1B genotypes and between two ALDH2 genotypes, although drinkers were 90.7% (11/12) among males with ADH1B *2*2 genotype.

## Discussion

The present study demonstrated that ADH1B *2 allele was more prevalent among Uzbeks (0.286) than among the Russians (0.087). ALDH2 *2 allele was 0.016 among 322 Uzbek alleles, and none among 46 Russian alleles. There were no significant differences in the allele frequency among healthy volunteers, PUD patients, and the other patients. Since the sample size was limited, no significant differences in drinking habits among the different genotypes were observed. The amount of alcohol drinking was not questioned.

We applied the same PCR method in this study as to our previous study, which demonstrated that ADH1B *2 allele and ALDH2 *2 allele among 453 Japanese were 0.793 and 0.306, respectively (Tamakoshi et al., 2003). The genotype frequencies of the present study subjects were in Hardy-Weinberg equilibrium. In addition, two ALDH2 *2 alleles were found for four Koreans in the subjects. Accordingly, it seemed unlikely that the results were influenced by the genotype method. The subjects were not randomly sampled from a region in Uzbekistan,

but from a case-control study of PUD. Since the allele frequencies did not differ among the different groups of subjects, who did not know their genotypes, selection bias may be limited, if any.

We used the official ethnicity based on their passport. Since actual ethnicity was difficulty to be defined, the definition based on the passport seemed one of the most reasonable approaches. Any ethnic groups have been mixed more or less during a long history, so that this study has been conducted. The ethnical mixture of their parents or grandparents seemed negligible because of the complicated social situations surrounding the ethnic groups in the 20th century. Accordingly, the allele distribution with the definition based on their passport may reflect the so-called Uzbeks.

The ADH1B*2 allele is not seen among Africans, is minor among Caucasians (0.006 among 90 Swedes to 0.052 among 115 Hungarians), and is major among East Asians (0.680 among 86 Chinese, 0.805 among 177 Koreans, and 0.778 among 634 Japanese) (Goedde et al., 1992; Yokoyama et al., 2002). This difference in the allele frequency between Caucasians and East Asians is one of the largest among the reported allele frequencies. The present data demonstrated that the allele frequency among Uzbeks was closer to that among Caucasians. Among the 23 Russians in this study, ADH1B *2 allele was 0.087, which was lower than the frequency reported for 23 Russian immigrants to Israel (0.174 by Hasin et al., 2002). Since the sample sizes of both studies were small, the difference in the allele frequency was not significant (Fisher's exact test, 0.354), indicating that studies with a larger size for Russians is required.

The ALDH2 *2 allele is also unique in terms of the geographic distribution. The geographical border of those with the *2 allele was not clear. In Mongolia and Tibet, the Lys allele frequency was 0.10 and 0.05, respectively (Chen et al., 1994). Among 179 Indians, the allele frequency was reported 0.020; 5 heterozygotes and 1 homozygote (Goedde et al., 1992), although another study reported that none had a *2 allele among 397 male Indians (Bhaskar et al., 2007). However, the allele was not found in Siberia and Northwest Asia (Komi, Zyriane, and Khanty). Three out of 117 Hungarians were reported to be heterozygous and none was homozygous; the allele frequency was 0.013 (Goedde et al., 1992). This study found that the *2 allele was also quite rare among Uzbeks; the allele frequency was 0.016. It suggested that Central Asia and East Europe might be the edge of populations with the *2 allele. Since the area from Central Asia to East Europe is very large, further studies are required to obtain more detail information on the exact allele distributions.

In conclusion, the present study was the first report demonstrating that the ADH1B *2 allele frequency of Uzbeks was closer to that of Caucasians, and that some Uzbeks had ALDH2 *2 allele. Since the ALDH2 *2 frequency among Uzbeks was found to be lower than that among Mongolians and similar to that among Hungarians, it seems natural to conclude that the spread was in fact from from East to West, as expected from many historical facts.

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