Differences in Genetic Variation of ADH2 and ALDH2 between Alcoholics and Healthy Persons in Korea

Yong Kyun Paik\textsuperscript{1}, Young Choi\textsuperscript{*}, Chun Geun Lee\textsuperscript{1} and In Kyu Kim\textsuperscript{3}

\textsuperscript{1}Department of Genetics, Hanyang University School of Medicine, Seoul 133-791, Korea
\textsuperscript{2}Department of Biology, College of Sciences, Yonsei University, Seoul 120-749, Korea
\textsuperscript{3}Department of Obstetrics and Gynecology, Yonsei University School of Medicine, Seoul 120-752, Korea

ABSTRACT

Alcohol dehydrogenases (ADHs) and aldehyde dehydrogenases (ALDHs) are the main enzymes responsible for the oxidation of ingested ethanol in human populations. In this study, the genotypes of the ADH2 and ALDH2 loci of 115 alcoholics (alcohol dependents) and 62 healthy controls were determined using a hybridization of PCR amplified genomic DNA with allele-specific oligonucleotide probes to examine the relationship between the variation of ADH2 and ALDH2 and the risk of developing alcoholism. The alcoholics had significantly lower frequencies of the ALDH2\textsuperscript{2} and ADH2\textsuperscript{2} alleles than did the controls; this corroborates that these alleles have inhibitory effects in the development of alcoholism. Our study revealed that the genotypic distributions between controls and alcoholics for ALDH2 and ADH2 genes were significantly different from those in pairwise random combination. We also investigated the effects of the ALDH2 genotypes on alcohol-associated symptoms and on drinking habits in ADH2 genotypes among control subjects, based on a self-reported questionnaire. The flushing frequency in the homozygous ALDH2 N/N group differed significantly depending on the ADH2 genotypes. A positive ethanol patch test was mainly determined by the ALDH2 genotypes. However, drinking habits were not significantly associated with both genotypes, except a comparison in the ALDH2 N/N group. In conclusion, our data support the idea that genetic variation in the enzymes that perform alcohol oxidation can substantially affect the risk of developing alcoholism.

Key words: Alcoholism, ADH2, ALDH2, Genetic Variation, Korean Population.

INTRODUCTION

Alcohol dehydrogenase (ADH E.C.1.1.1.1.) and aldehyde dehydrogenase (ALDH E.C.1.2.1.3.), which catalize the oxidation of ingested ethanol to acetaldehyde and then to acetic acid respectively, are thought to be the principal enzymes responsible for alcohol metabo-
lism in humans (Goedde et al., 1979; Agarwal and Goedde, 1990). Each enzyme exists as multiple, genetically determined molecular forms (Smith, 1986).

The oxidation of acetaldehyde to acetate is believed to be catalyzed primarily by ALDH2, the low-\(K_m\) form of ALDH that is constitutively present in mitochondria. The gene for this homotetrameric enzyme is located on chromosome 12 (Braun et al., 1987). A transition mutation in ALDH2 produces a deficiency in ALDH2 activity (Yoshida et al., 1984). The deficient allele ALDH2\(^d\) (Glu147-Lys147) is dominant over the normal ALDH2\(^a\) allele (Crabb et al., 1989; Singh et al., 1989). An ALDH2 deficiency has been detected in almost none of the Caucasoid, Negroid, and Australian aboriginal populations tested so far (Agarwal and Goedde, 1992). It is associated with facial flushing and other adverse reactions, such as palpitations, tachycardia, and muscle weakness (Wolf, 1972; Harada et al., 1981). In individuals with inactive ALDH2, delayed oxidation of acetaldehyde in acetate after alcohol consumption results in transient hyperacetaldehydemia, the main cause for a flushing response in many Asians (Harada et al., 1985; Higuchi et al., 1996). This response to ethanol ingestion presumably lowers the risk of alcoholism as a result of slow acetaldehyde removal. Although some individuals with deficient ALDH2 do become alcoholics, the mechanism by which they become alcoholic is not known.

The oxidation of ethanol by ADH is caused by homo- and hetero-dimeric allozymes containing \(\alpha\), \(\beta\), and \(\gamma\) subunits encoded by ADH1, ADH2, and ADH3 genes closely linked on chromosome 4. Of special interest is ADH2 allozyme, which is polymorphic in diverse populations and which differs in its kinetic properties. It has been reported that the \(\beta 2\beta 2\) allozyme encoded by the ADH2\(^a\) allele (Arg129-His129) has much higher ethanol-oxidizing activity than \(\beta 1\beta 1\) allozyme encoded by ADH2\(^d\) allele does (Bosron and Li, 1986). These differences have been suggested to explain why lower ADH2\(^a\) allele frequencies exist in alcoholics than in nonalcoholic controls (Thomasson et al., 1991). The higher activities of \(\beta 2\) subunits cause higher blood acetaldehyde levels after drinking and may inhibit heavy drinking in individuals with these subunits. The atypical or mutant, superactive allele of the alcohol dehydrogenase \(\beta\)-subunit (ADH2\(^s\)) is highly prevalent in Mongoloids, but is less common in Caucasoids and Negroids (Goedde et al., 1992).

Previous investigations over the last two decades suggest that genetic variation in both ADH and ALDH influences both drinking behavior and the risk of developing alcoholism in some Asian populations (Takeshita et al., 1996; Shen et al., 1997; Paik et al., 1999). In this study, we investigated whether alcohol-metabolizing enzyme polymorphisms involving ADH2 and ALDH2 are associated with the development of alcoholism in Koreans. The results elucidate how this polymorphism influences drinking behavior in the present population.

**MATERIALS AND METHODS**

There were 62 nonalcoholic control subjects in this study (52 men and 10 women, ages 19 ~ 27 years) living in Seoul, all of them from the same junior class of medical school students. Information on their drinking behavior was obtained by a self-reported questionnaire, before the 70% ethanol patch test (Muramatsu et al., 1989). The 115 alcoholic