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Genetic Polymorphism of Aldehyde Dehydrogenase 2 (*ALDH2*) in a Chinese Population: Gender, Age, Culture, and Genotypes of *ALDH2*

Huai-Rong Luo,[1,2] **Yedy Israel,**[3,4] **Guang-Chou Tu,**[3]
C. J. Peter Eriksson,[5] **and Ya-Ping Zhang**[1,2,6]

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INTRODUCTION

Not only is alcoholism one of the world's major public health problems because of the significant morbidity caused by alcohol abuse disorder but it is also a big social problem. An atypical allele (*ALDH2*487Lys*, former name *ALDH2*2*) in low *K*m aldehyde dehydrogenase (ALDH2), which is highly prevalent in Asian populations, is associated with drinking behavior and some alcohol-related diseases (Yoshida, 1994; Yokoyama *et al*., 2003). There are some differences in its frequency among Asian populations of different geographic areas. In our previous study, the frequency of the *ALDH2*487Lys* allele was much lower (12%) in Wuhan Han Chinese and much higher (31%) in Guangdong Han Chinese populations than that reported in other Oriental populations (Chen *et al*., 1999; Luo *et al*., 2001; Luo and Zhang, 2004).

Recent developments in gene therapy allow a long-term inhibition of gene expression. Garver *et al*. (2001) asserted that antisense oligonucleotides

[1] Laboratory of Cellular and Molecular Evolution, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming 650223, China.
[2] Laboratory for Conservation and Utilization of Bioresources, Yunnan University, Kunming 650091, China.
[3] Department of Pathology, Anatomy, and Cell Biology and Alcohol Research Center, Thomas Jefferson University, Philadelphia, Pennsylvania.
[4] Department of Pharmacology, Faculty of Chemical and Pharmaceutical Sciences, and Millennium Institute of Advanced Studies in Cell Biology and Biotechnology, University of Chile, Chile.
[5] Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland.
[6] To whom correspondence should be addressed; e-mail: zhangyp1@263.net.cn.

inhibit ALDH2 gene expression, increase acetaldehyde levels following ethanol administration, and markedly reduce alcohol consumption in animals. Before any attempts are made to modify in vivo gene expression, however, it should be asked whether the low ALDH2 activity in subjects with *ALDH2*487Lys* has health implications for the general population. If the *ALDH2 Glu487Lys* genotypes are different between gender groups, and if the *ALDH2*487Lys* mutation influences longevity, different age groups would show changes in the prevalence of *ALDH2*487Lys*. A lower prevalence of *ALDH2*487Lys* in the elderly than in infants would suggest an increased mortality due to the atypical allele. Here, we determined the prevalence of the *ALDH2*487Lys* allele in males and females, infants (<1 year old), young adults (25–35 years old), and old adults (>70 years old) in China.

MATERIALS AND METHODS

This study surveyed 648 unrelated Yunnan Han Chinese individuals of different genders and ages (Table I). All the samples are healthy individuals who were attending a medical university hospital for routine checkups. Informed consent was requested from the adults and from the parents of the infants for the small aliquots of blood used in this study. The ranges for the three age groups were from 4 days to 1 year old (infant), 25 years to 35 years (young), and older than 70 years (old). Genomic DNA was extracted from whole blood by the standard phenol/chloroform method. The determination of *ALDH2 Glu487Lys* locus genotypes was performed by the mismatch amplification assay method (Cha *et al*., 1992), as adapted by Luo *et al*. (2001). Then, the frequencies of the *Glu487Lys* genotypes and alleles were determined assuming codominant inheritance. Hardy-Weinberg equilibrium was tested by means of chi-square tests with the HWSIM program

Table I. The Frequencies of *ALDH2* Glu487Lys Genotypes and Alleles in Different Gender and age Categories

			Genotypes frequencies				Alleles frequencies	
		N	GG[a]	GA	AA	GA + AA	G	A
Gender	Female	204	133 (65.20)	61 (29.90)	10 (4.90)	71 (34.80)	(80.15)	(19.85)
	Male	444	308 (69.37)	121 (27.25)	15 (3.38)	136 (30.63)	(83.00)	(17.00)
Age	Infant	100	69 (69.00)	27 (27.00)	4 (4.00)	31 (31.00)	(82.50)	(17.50)
	Young	315	214 (67.94)	89 (28.25)	12 (3.81)	101 (32.06)	(82.06)	(17.94)
	Old	233	158 (67.81)	66 (28.33)	9 (3.86)	75 (32.19)	(81.97)	(18.03)
Total		648	441 (68.06)	182 (28.09)	25 (3.85)	207 (31.94)	(82.09)	(17.91)

Note: All values in the parenthesis are percentages. No significant differences were found ($p > 0.05$).
[a]GG is the "normal" genotype, GA the heterozygote, and AA the homozygote abnormal.

(http://krunch.med.yale.edu/hwsim/). Afterward, gender and age were included as independent variables for further statistical calculation. The statistical significance of the *Glu487Lys* genotype and allele frequency variables between the independent variables was evaluated through chi-square tests using the program SPSS version 11.5 (SPSS Inc., Chicago, IL).

RESULTS

All *ALDH2 Glu487Lys* genotype frequencies fit Hardy-Weinberg expectations according to χ^2-tests ($p > 0.05$) in total unrelated Chinese. The frequencies of the genotypes and alleles for the samples are given in Table I. Since the mutation in *ALDH2 Glu487Lys* is dominant (Crabb *et al*., 1989; Singh *et al*., 1989; Xiao *et al*., 1995), the frequencies of the individuals with the *ALDH2*487Lys* genotypes are listed in a single column in each group (GA + AA). The frequencies of the *ALDH2*487Glu*/*Glu* (GG), *ALDH2*487Glu*/*Lys* (GA), and *ALDH2*487Lys*/*Lys* (AA) genotypes in the 648 subjects were 68.06% (441/648), 28.09% (182/648), and 3.85% (25/648), respectively. The frequency for the atypical *ALDH2*487Lys* allele in the total samples was 17.91%. No significant difference in the frequency of *ALDH2 Glu487Lys* genotypes was found between men and women in the overall Chinese population ($p > 0.05$). The overall frequency of *ALDH2 Glu487Lys* genotypes did not differ significantly among the infant, young, and old groups ($p > 0.05$).

DISCUSSION

The atypical allele (*Glu487Lys*) with a low *K*m aldehyde dehydrogenase (ALDH2) is associated with drinking behavior and some alcohol-related diseases (Yoshida, 1994; Yokoyama *et al*., 2003). In order to understand the relation among age, gender, and the genotypes of *ALDH2*, we have determined the *ALDH2 Glu487Lys* genotypes in Chinese samples from different gender and age groups.

In China, alcohol consumption is 6∼7 times higher among men than among women (Shi, 2002). We found no gender-related differences, however, in the *ALDH2 Glu487Lys* genotype frequencies. The low alcohol consumption in women might be caused by Chinese culture and/or by other biological factors.

We also failed to show any age-related differences in the *ALDH2 Glu487Lys* genotype frequencies. The present result of the age-related *Glu487Lys* genotypes gives some useful information for further studies on the *ALDH2 Glu487Lys* genotypes. At the beginning of the experiment, some differences in the allele frequencies were expected between the age groups because the atypical allele has lost the important function of ALDH2 and is strongly related to some diseases, even some types of cancer (Seitz *et al*., 2001; Yokoyama *et al*., 2003). We did not find any frequency difference, however, in the old group when compared with the infant

and young groups (Table 1). One possible reason is that in individuals who have atypical alleles, drinking behavior is greatly reduced following a small alcohol intake, thus discouraging more alcohol drinking. In other words, the atypical allele could not affect overall survival of individuals, because individuals with the mutation have an inborn avoidance of alcohol. Thus, the existence of an atypical allele *ALDH2*487Lys* does not affect the mortality rate in the population. The data obtained strongly suggest that the allele *ALDH2*487Lys* does not increase mortality in a 70-year span in the general population. The above data indicate that long-term therapeutic modifications to inhibit *ALDH2* gene expression or ALDH2 activity would not have an overall detrimental effect on demographic health and could be considered as adjuncts in the treatment of alcoholism.

Disulfiram, which inhibits aldehyde dehydrogenases, is an effective drug in the treatment of alcoholism (Chick *et al*., 1992; Brewer *et al*., 2000), but it requires daily administration, binds nonspecifically to the sulfhydryl groups of proteins and has side effects such as orthostatic hypotension, sensory and motor neuropathies, and optic neuritis (Peachey and Annis, 1989; Fuller and Gordis, 2004), all of which reduce patient compliance. The possibility of long-term gene therapeutic approaches that would not require compliance supervision, based on the marked protection against alcoholism of individuals who naturally present a low ALDH2 activity, is of potential significance. The mutation *ALDH2*487Lys* allele is not deleterious but is of great benefit to human health.

Alcoholism is a multifactorial disorder, and collecting the affected samples for the association analysis is very difficult. To trace the origin and perpetuation of the East Asian special *ALDH2*487Lys* allele, more genotyping data from normal individuals for the Asian subpopulations is essential. Collection of affected samples will be facilitated by the present study, which showed that the samples could be collected within local populations without consideration of gender or age differences. These data also show that samples can be collected to analyze for the *ALDH2 Glu487Lys* genotype frequency variance among different Asian subpopulations without consideration of gender or age in future studies. The knowledge derived will be of value in arriving at a better understanding of the origin of the atypical *ALDH2*487Lys* allele and for the diagnosis, treatment, and prevention of ALDH2-related diseases in East Asians.

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