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Application of *aldehyde dehydrogenase 2 (ALDH2)* Genetic Diagnosis in Support of Decreasing Alcohol Intake

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Abstract: Application of *aldehyde dehydrogenase 2 (ALDH2)* Genetic Diagnosis in Support of Decreasing Alcohol Intake: Yasuhiro KOMIYA, *et al*. Division of Public Health, Department of Social Medicine, Faculty of Medicine, University of Miyazaki—Encouraging behavioral changes to decrease alcohol intake is not easy from the standpoint of health support. This study was conducted to examine whether the genetic diagnosis of *ALDH2* polymorphism is useful in supporting those who want to decrease their alcohol intake. The participants in this study were 329 male employees who wanted to know the result of their *ALDH2* genotype. We divided the 329 participants randomly into two groups. One was the "notified group" (n=157), and the other was the "non-notified group" (n=172). The subjects belonging to the "notified group" were informed of the results of the *ALDH2* genotype diagnosis in April, 2003. Drinking habits and laboratory data were obtained before and after notification of the *ALDH2* genotype. Among those with genotype *ALDH2*1/*1*, there was no significant change in drinking frequencies, nor was there any significant decline in liver function laboratory data in either of the groups before and after notification of the genotype. However, weekly alcohol intake tended to increase compared to that before notification. On the other hand, with regard to those with genotype *ALDH2*1/*2*, no significant changes in drinking frequencies or liver function laboratory data were evident in either group before and after notification of the genotype. However, the weekly alcohol intake tended to increase in the non-notified group, whereas it tended to decrease in the notified group. Although the result was not significant, it is suggested that, with further study and an increased sample size, the genetic diagnosis may be found to be useful.

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Currently, in the field of occupational health, management of lifestyle diseases has become one of the most important issues. Lifestyle diseases, including cancer, occur as a result of interactions between external factors, including smoking, drinking, diet and exercise, and internal factors that are genetically predisposed.

In recent years, disease susceptibility, which indicates vulnerability to various environmental factors, has been elucidated at the gene level using molecular epidemiology. Aldehyde dehydrogenase 2 (ALDH2) plays an important role in the metabolism of acetoaldehyde[1]. Yokoyama *et al*. reported that among alcoholics and heavy drinkers, those with genotype *ALDH2*1/*2* (low enzyme activity) had a 7 to 12 times higher risk of developing esophageal cancer than those with *ALDH2*1/*1* (normal enzyme activity)[2].

In addition, Yokoyama reported in 2002 that the same tendency was observed with regard to the incidence of esophageal cancer among light (odds ratio (OR): 5.82, 95% confidence interval (95%CI): 1.59–21.38) and moderate drinkers (OR: 10.01, 95% CI: 5.13–19.52)[3].

Encouraging behavioral changes to decrease alcohol intake is not easy from the standpoint of health support. One reason for the difficulty is that a decrease alcohol intake is not likely to be recognized as a contributing factor with tangible benefits to the individual. In other words, guidance without considering a person's alcohol susceptibility may not contribute to strong motivation to decrease alcohol intake.

This study was conducted to examine whether the genetic diagnosis of *ALDH2* polymorphism is useful in supporting those who want to decrease their alcohol intake.

Material and Methods

Subjects

The participants of this study were 329 (51.6%) of 637 male employees working at a manufacturing factory in Japan who wanted to know the result of their *ALDH2* genotype. The subjects consented to participate in this study, and consented to offer their DNA for the study. In our previous study, multiple regression analysis showed that the number of respondents who "wanted to know the results of the genetic diagnosis" was significantly higher among those with a high CAGE test score (OR=1.96, 95%CI 1.42–2.68) and those who drank five or more times per week (OR=1.40, 95%CI 1.07–2.68)[4].

We divided the 329 participants randomly into two groups: the "notified group", the members of which were notified of the result of the *ALDH2* genotype earlier (n=157); and the "non-notified group", the members of which were notified of the results of the *ALDH2* genotype at a later date (n=172). There was no significant difference in the number of subjects in each group.

The subjects belonging to the "notified group" were informed of the results of the *ALDH2* genotype diagnosis in April 2003. We communicated the results during individual interviews and explained the points to keep in mind concerning health to each interviewee who had *ALDH2* genotypes (*ALDH2*1/*1*: Please be careful of liver dysfunction, liver cirrhosis and alcoholism; *ALDH2*1/*2*: The risk for several kinds of cancer is higher than the *ALDH2*1/*1* genotype; *ALDH2*2/*2*: Be careful of acute alcoholism).

We were able to notify the results of the *ALDH2* genotypes to 101 participants out of the 157 subjects in the "notified group" (64.3%) within the predetermined period and could follow-up 85 participants out of the 101 who were notified of the results (54.1%). We were able to follow-up 130 participants out of the 172 who belonged to the "non-notified group" (75.6%). The main reasons that we were not able to notify the results or do follow-up with the rest of the participants were changes in their workplace or their retirement. There was no significant difference between the follow-up rates of each group.

Drinking habits and laboratory data (GOT, GPT, γGTP) were obtained before and after notification of the *ALDH2* genotype from regular medical health check-ups held in October 2002 and October 2004.

All participants were given an explanation of the nature of the study and their informed consent was obtained. This study was approved by the ethics committees of the University of Miyazaki.

Genotyping

Genomic DNA was isolated from peripheral leukocytes by proteinase K digestion and phenol/chloroform extraction. The genotypes of *ALDH2* were identified as the homozygous genotype of normal *ALDH2*1/*1*, the homozygous genotype of inactive *ALDH2*2/*2* and the heterozygous genotype of normal and inactive *ALDH2*1/*2* by the method of Harada and Zhang[5].

Statistical analysis

The average weekly alcohol intake (g), GOT, GPT, and logγGTP before notification were compared with those after notification using t-test in both the notified and non-notified groups. In addition, we also used a non-parametric comparison to compare the weekly alcohol intake before and after notification. Values of $p<0.05$ were considered statistically significant. SPSS for Windows software (version 11.0J, SPSS Japan, Tokyo, Japan) was used for statistical analyses.

Results

Table 1 outlines the *ALDH2* genotype frequencies and mean age of each *ALDH2* genotype. There were no significant differences with regard to genotype frequencies and mean age between the notified and the non-notified groups.

The proportion of persons who drank once or more per week relative to those who drank 6 times or more per week before (October 2002) and after (October 2004) notification are shown in Table 2. Before notification of the genotype, the proportion of the participants drinking once or more per week were 87.0% for *ALDH2*1/*1*, 53.6% for *ALDH2*1/*2*, and 0% for *ALDH2*2/*2* in the notified group, and 87.5% for *ALDH2*1/*1*, 53.8% for *ALDH2*1/*2*, and 0% for *ALDH2*2/*2* in the non-notified group. Furthermore, prior to notification of the genotype, the proportion of the participants drinking 6 times or more per week were 50.0% for *ALDH2*1/*1*, 25.0% for *ALDH2*1/*2*, and 0% for *ALDH2*2/*2* in the

Table 1. *ALDH2* genotype frequencies among the notified group and the non-notified group

	*ALDH2*1/*1*	*ALDH2*1/*2*	*ALDH2*2/*2*
Notified group	54 (63.5%)	28 (32.9%)	3 (3.5%)
(n=85)	39.0 ± 6.1 yr old	41.0 ± 4.4 yr old	35.3 ± 8.3 yr old
Non-notified group	88 (67.7%)	39 (30.0%)	3 (2.3%)
(n=130)	38.9 ± 6.4 yr old	40.4 ± 5.5 yr old	48.3 ± 6.7 yr old

Table 2. Ratios of persons drinking once or more per week to those drinking 6 times or more per week before (October 2002) and after (October 2004) notification

			*ALDH2*1/*1*	*ALDH2*1/*2*	*ALDH2*2/*2*
Notified group (n=85)	≥1 per wk	Oct. 2002	47/54 (87.0%)	15/28 (53.6%)	0/3 (0%)
		Oct. 2004	46/54 (85.2%)	15/28 (53.6%)	0/3 (0%)
	≥6 per wk	Oct. 2002	27/54 (50.0%)	7/28 (25.0%)	0/3 (0%)
		Oct. 2004	25/54 (46.3%)	9/28 (32.1%)	0/3 (0%)
Non-notified group (n=130)	≥1 per wk	Oct. 2002	77/88 (87.5%)	21/39 (53.8%)	0/3 (0%)
		Oct. 2004	80/88 (90.9%)	17/39 (43.6%)	0/3 (0%)
	≥6 per wk	Oct. 2002	52/88 (59.1%)	9/39 (23.1%)	0/3 (0%)
		Oct. 2004	47/88 (53.4%)	11/39 (28.2%)	0/3 (0%)

Table 3. Weekly alcohol intakes (g) before and after notification

			A*LDH2*1/*1*	*ALDH2*1/*2*
Notified group	Weekly alcohol intake (g)	Oct. 2002	269.0 ± 215.9	210.7 ± 227.8
		Oct. 2004	291.3 ± 309.2	190.0 ± 164.9
Non-notified group	Weekly alcohol intake (g)	Oct. 2002	287.7 ± 204.5	218.3 ± 216.0
		Oct. 2004	306.9 ± 230.2	252.1 ± 230.5

Table 4. GOT, GPT and log(γGTP)(IU/L) before and after notification

			*ALDH2*1/*1*	*ALDH2*1/*2*	*ALDH2*2/*2*
Notified group	GOT	Oct. 2002	24.0 ± 6.5	22.2 ± 6.9	20.0 ± 3.0
		Oct. 2004	25.0 ± 9.8	22.3 ± 7.9	20.3 ± 1.2
	GPT	Oct. 2002	34.8 ± 20.0	32.6 ± 13.6	25.0 ± 7.9
		Oct. 2004	38.5 ± 24.9	34.5 ± 14.6	27.3 ± 4.2
	logγGTP	Oct. 2002	1.71 ± 0.30	1.65 ± 0.27	1.39 ± 0.12
		Oct. 2004	1.74 ± 0.28	1.68 ± 0.24	1.34 ± 0.04
Non-notified group	GOT	Oct. 2002	22.4 ± 9.2	22.0 ± 7.7	19.7 ± 7.0
		Oct. 2004	22.3 ± 7.7	21.8 ± 6.3	20.3 ± 6.7
	GPT	Oct. 2002	30.2 ± 17.8	28.5 ± 13.0	35.7 ± 19.7
		Oct. 2004	33.4 ± 17.9	31.1 ± 16.1	30.0 ± 6.1
	logγGTP	Oct. 2002	1.72 ± 0.27	1.62 ± 0.23	1.63 ± 0.20
		Oct. 2004	1.76 ± 0.29	1.63 ± 0.21	1.56 ± 0.08

notified group, and 59.1% for *ALDH2*1/*1*, 23.1% for *ALDH2*1/*2*, and 0% for *ALDH2*2/*2* in the non-notified group. The investigation performed after notification of the genotype demonstrated that there was no significant change in drinking frequency between either group in comparison with before notification of their genotype.

We selected those participants who drank once or more per week from both groups, and compared their weekly alcohol intake before and after notification of the *ALDH2* genotype (Table 3). The weekly alcohol intake after notification tended to increase from that before notification among those with genotype *ALDH2*1/*1* in the notified (269.0 ± 215.9 (g)→291.3 ± 309.2 (g)) and non-notified groups (287.7 ± 204.5 (g)→306.9 ± 230.2 (g)) although these increases were not statistically significant. On the other hand, among those with the genotype *ALDH2*1/*2*, the weekly alcohol intake after notification tended to increase among the non-notified group (218.3 ± 216.0 (g)→252.1 ± 230.5 (g)) but tended to decrease among the notified group (210.7 ± 227.8 (g)→190.0 ± 164.9 (g)) compared with before notification. However, these changes were not statistically significant. In addition, we also used a non-

parametric comparison to compare the weekly alcohol intake before and after notification. Table 4 outlines the changes of GOT, GPT and log (γGTP) before and after notification of the *ALDH2* genotype in the notified and non-notified groups. No statistically significant changes in GOT, GPT or log (γGTP) were evident among those subjects with either genotype between before and after notification of the *ALDH2* genotype.

Discussion

Heavy drinking increases the risk of cerebral hemorrhage and cancer, including oral cavity cancer, esophageal cancer and hepatocellular carcinoma[6, 7]. Also, it is often observed that patients with diabetes mellitus who drink every day have difficulty in controlling their blood sugar level. Therefore, support for decreasing alcohol intake is one of the most important issues in preventive medicine.

The allele frequencies of *ALDH2* polymorphism are *1=0.710, *2=0.290 in the Japanese population[8] and *1=1.00, *2=0.00 in the Caucasian population[9]; and the difference between them is widely known. Higuchi reported that the risk for alcoholism was higher among Japanese with *ALDH2*1/*1*, significantly lower among those with *ALDH2*1/*2*, and that no alcoholics were found with the *ALDH2*2/*2* genotype[10]. Yokoyama *et al*. reported that among alcoholics and heavy drinkers, those with the genotype *ALDH2*1/*2* (low enzyme activity) had a 7 to 12 times higher risk of developing esophageal cancer compared with those with genotype *ALDH2*1/*1* (normal enzyme activity)[2]. These findings also indicate that it is highly desirable to provide tailored support for decreasing alcohol intake, by informing individuals of their alcohol susceptibility as predetermined by the *ALDH2* genotype. Yokoyama and Takeshita reported that ADH2 polymorphism is associated with ethanol sensitivity and esophageal cancer susceptibility[3, 11]. We selected only *ALDH2* polymorphism in this study, because we considered that if we notified the subjects of plural genetic diagnoses, such as *ADH2* and *ALDH2*, the explanation would become complicated and understanding it would become difficult. Although support for decreasing alcohol intake using the ethanol patch test has been performed in Japan, the most important benefit of genetic diagnosis is the persuasive power that leads to absolute objectivity.

The results of this study show that among those with genotype *ALDH2*1/*1*, there was no significant change in drinking frequencies, nor was there any significant decline in liver function as determined by laboratory data in either of the groups between before and after notification of the genotype. However, weekly alcohol intake tended to increase compared to that before notification. We should explain that we do not interpret this as meaning that those with genotype *ALDH2*1/*1* can drink much more than those with genotype *ALDH2*1/*2*.

On the other hand, with regard to those with genotype *ALDH2*1/*2*, no significant changes in drinking frequencies or liver function as determined by laboratory data were evident in either group between before and after notification of the genotype. However, the weekly alcohol intake tended to increase in the non-notified group, whereas it tended to decrease in the notified group.

In Japan, the burden of work on individuals has been on the rise, and many companies have introduced a performance-based pay system. The results of our investigation demonstrate that the number of workers who try to cope with their stress by drinking has also been increasing. Therefore, drinking frequency and alcohol intake are likely to increase in the above-mentioned situation. Thus, the finding that the weekly alcohol intake of those with genotype *ALDH2*1/*2* among the notified group tended to decrease after notification is likely to be worthy of recognition.

Although the result was not significant, it is suggested that, with further study and an increased sample size, the genetic diagnosis of the *ALDH2* polymorphism may be found to be useful in supporting those who want to decrease their alcohol intake, and those with genotype *ALDH2*1/*2* in particular.

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References

1) S Harada, DP Agarwal and HW Goedde: Aldehyde dehydrogenase deficiency as cause of facial flushing reaction to alcohol in Japanese. Lancet 2, 982 (1981)
2) A Yokoyama, T Muramatsu, T Ohmori, S Higuchi, M Hayashida and H Ishii: Esophageal cancer and aldehyde dehydrogenase-2 genotypes in Japanese males. Cancer Epidemiol Biomarkers Prev 5, 99–102 (1996)
3) A Yokoyama, H Kato, T Yokoyama, T Tsujinaka, M Muto, T Omori, T Haneda, Y Kumagai, H Igaki, M Yokoyama, H Watanabe, H Fukuda and H Yoshimizu: Genetic polymorphism of alcohol and aldehyde dehydrogenases and glutathione S-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. Carcinogenesis 23, 1851–1859 (2002)
4) Y Komiya, H Nakao, Y Kuroda, K Arizono, A Nakahara and T Katoh: Consciousness survey regarding genetic diagnosis of glutathione S-transferase M1 (GSTM1) and aldehyde dehydrogenase 2 (ALDH2) polymorphism. San Ei Shi 47, 204–209 (2005)
5) S Harada and S Zhang: New strategy for detection of ALDH2 mutant. Alcohol Alcoholism Suppl 1A, 11–13 (1993)
6) K Reynolds, B Lewis, JD Nolen, GL Kinney, B Sathya and J He: Alcohol consumption and risk of stroke:a

meta-analysis. JAMA 289, 579–588 (2003)
7) The WCRF/AICR Expert Report. Food, Nutrition and the prevention of cancer: a global perspective, provides the vital scientific evidence for all of AICR research and education programs. Washington, DC: BANTA Book Group, 1997.
8) T Takeshita, K Morimoto, XQ Mao, T Hashimoto and J Furuyama: Phenotypic differences in low Km aldehyde dehydrogenase in Japanese workers. Lancet 8848, 837–838 (1993)
9) HW Goedde, DP Agarwal, G Fritze, D Meier-Tackmann, S Singh, G Beckmann, K Bhatia, LZ Chen, B Fang and R Lisker: Distribution of ADH2 and ALDH2 genotypes in different populations. Hum Genet 88, 344–346 (1992)
10) S Higuchi: Polymorphisms of ethanol metabolizing enzyme genes and alcoholism. Alcohol Alcohol Suppl 2, 29–34 (1994)
11) T Takeshita, XQ Mao and K Morimoto: The contribution of polymorphism in the alcohol dehydrogenase beta subunit to alcohol sensitivity in a Japanese population. Hum Genet 97, 409–413 (1996)