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REGULAR ARTICLE

Associations between aldehyde dehydrogenase 2 (*ALDH2*) genetic polymorphisms, drinking status, and hypertension risk in Japanese adult male workers: a case–control study

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Abstract
Objectives We sought to identify associations between aldehyde dehydrogenase 2 (*ALDH2*), alcohol consumption, and hypertension in Japanese men.
Methods The study participants were 1,225 male Japanese workers. We collected lifestyle information, body measurements, blood biochemical parameters, blood pressure measurements, and *ALDH2* genotyping data during medical examinations conducted between March 2004 and January 2005 at a work facility and an affiliated company. Lifestyle data on alcohol intake and smoking were collected using self-administered questionnaires at the same time as when the aforementioned measurements were obtained.
Results The genotype frequencies of *ALDH2* genetic polymorphisms were 62.6, 32.7, and 4.7 % for **1/*1*, **1/*2*, and **2/*2*, respectively. Systolic blood pressure and diastolic blood pressure in the **1/*2* or **2/*2* group were significantly lower than those in the **1/*1* group ($P < 0.001$). Multiple regression analysis (stepwise method) for blood pressure according to *ALDH2* genetic polymorphism revealed that the amount of daily alcohol intake affected systolic blood pressure in participants who harbored the *ALDH2* genetic polymorphism **1/*2* or **2/*2*.
Conclusions The interaction between alcohol intake and *ALDH2* genetic polymorphisms might affect systolic blood pressure in adult male workers.

Keywords Aldehyde dehydrogenase 2 · Drinking · Hypertension · Polymorphism · Genetic association studies · Japanese

Introduction

Hypertension (HT) is recognized as an established and one of the strongest risk factors for cardiovascular disease (ischemic heart disease and stroke). In 2010, 43 million people in Japan (23 million males and 20 million females) were estimated to be hypertensive patients (systolic/diastolic BP ≥140/90 mmHg) or to be under antihypertensive medication; this estimate was based on NIPPON DATA 2010 and the 2010 National Census of Japan [1, 2]. Because of concerns regarding an increase in HT with aging in the future, factors responsible for HT are considered to represent a critical public health problem. HT is a multifactor disease that develops through the interaction of numerous genetic and lifestyle factors, much like several lifestyle-related diseases [3]. Recently, the effect of a healthy influence on various lifestyle factors related to HT was elucidated at a gene level using molecular epidemiology techniques [4]. In terms of lifestyle, the risk of HT is increased by alcohol intake, smoking, obesity, and lack of exercise [5]. Epidemiological studies have revealed that alcohol intake, in particular, is a leading risk factor for HT [6–10].

Alcohol metabolism has been shown to be affected by polymorphisms in the genes encoding aldehyde dehydrogenase 2 (*ALDH2*), alcohol dehydrogenase 2 (*ADH2*), and

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cytochrome P450 2E1 (*CYP2E1*) [11]. Among these various genetic polymorphisms, *ALDH2* polymorphisms have been reported to be most strongly related to alcohol metabolism [12]. Differences in the pharmacokinetics of alcohol absorption and elimination are, in part, genetically determined. Polymorphic variants of the two main enzymes responsible for ethanol oxidation in liver, ADH and ALDH, have been identified. The frequency of occurrence of these variants, which have been shown to display strikingly different catalytic properties, differs among distinct ethnic populations [13]. Alcohol is oxidized in vivo by ADH into acetaldehyde, which is further oxidized by ALDH2 into acetic acid and metabolized by the citric acid cycle. Multiple forms of ALDH are present in the liver, and the mitochondrial form of the enzyme, which is encoded by the *ALDH2* locus on Chromosome 12, has a very low Km for acetaldehyde and is considered to be responsible for oxidizing most of the acetaldehyde generated during alcohol metabolism. The sequences of the two distinct forms of ALDH2 differ only by a Glu-to-Lys substitution at position 487, a single change that results in a complete loss of ALDH activity [14–18].

Alcohol intake is a commonly accepted behavior, but it potently affects health. Numerous cross-sectional and longitudinal studies have consistently shown that heavy alcohol intake is related to elevated blood pressure and to the prevalence and incidence HT [6, 7]. Furthermore, several prospective studies have also reported a relationship between alcohol intake and the development of HT [8–10]. However, only a few epidemiological studies have addressed the association between *ALDH2* genetic polymorphism and the state of HT [19, 20], and thus several questions remain unanswered. Therefore, in this study, we examined how *ALDH2* genetic polymorphisms and alcohol intake—including the quantity of intake—affect the state of high blood pressure.

Materials and methods

Participants and methods

The study initially recruited 1,900 male workers of a manufacturing facility and an affiliated company in Kyushu district, Japan. Of the 1,900 workers, 1,230 agreed to participate in the study and follow its guidelines. Among these 1,230 participants, we analyzed 1,225 workers for whom complete data were available on lifestyle, body measurements, blood biochemical composition, blood pressure, and *ALDH2* genotyping; the data were collected during medical examinations performed between March 2004 and January 2005 at the work facility and company. The lifestyle data on alcohol intake and smoking were collected using a self-administered questionnaire at the same time as when the aforementioned measurements were obtained. We used the remaining blood from the medical examination performed at the company as a sample for gene analysis. The participants ranged in age from 19 to 64 years (mean 42.6 $\pm$ 8.6 years). Height and weight were measured during a comprehensive health check, and body mass index (BMI) was calculated as weight (in kilograms) divided height (in meters) squared. As part of the blood biochemical inspection, we measured the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride (TG). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using the right or left upper arm while the participants were seated; the participants were allowed to rest quietly and calmly for $\geq$5 min before SBP and DBP were measured using an automatic sphygmomanometer. SBP and DBP were measured twice and then averaged. All data were anonymized, and we followed the ethics guidelines for human genome/gene analysis research [21] endorsed by the Japanese government. The study protocol was approved by the ethics committee of Kumamoto University Graduate School of Medical Sciences (no. 151; September 16, 2009), and all participants provided written informed consent.

Lifestyle assessment

Information related to alcohol intake was obtained using the self-administered questionnaire, which asked questions regarding the participants' drinking status and also their drinking frequency and amount of daily intake. Consumption of various types of alcoholic beverage—Japanese sake (such as rice wine), beer, shochu, and wine—was determined from the average number of drinks per day, which was then converted into a pure alcohol quantity. Daily alcohol intake was estimated as the summed amount of pure alcohol consumption (grams per drinking session) of Japanese sake, beer, shochu, and wine among current and former regular drinkers. Next, the amount of daily alcohol intake was separated into the following four categories based on daily pure alcohol consumption: no intake, and 6–15, 16–32, and >33 g/day. The participants' smoking status was categorized as follows: non-smoker, 1–20 cigarettes/day, and >21 cigarettes/day.

Determination of ALDH2 genotypes

The blood remaining from the medical examination (2–4 mL) was obtained with permission. DNA was extracted from 100 μL of white blood cell-rich plasma by using a DNA extraction kit (Wako Pure Chemical Industries, Osaka,

Japan). Takeshita and colleagues [13] reported that exon 12 of *ALDH2* was amplified following 33 cycles of PCR (1 min at 94 °C, 10 s at 52 °C, and 30 s at 72 °C). The same amplification primers were used here, except that in one primer (5′-CCACACTCACAGTTTTCTCTT-3′), an adenine was substituted with a thymine (at the underlined portion) to create a *Ksp6321* recognition site (5′-CTCTTC) in the typical allele. PCR products were ethanol-precipitated and redissolved in distilled water. The reaction mixture containing the PCR products, 2–3 U of *Ksp6321* (Nippon Roche, Tokyo, Japan), and the reaction buffer was incubated at 37 °C for 3–6 h, and then ethanol-precipitated. Resuspended samples were electrophoresed on gels containing 3.5 % NuSieve GTG agarose (BioWhittaker Molecular Applications, Rockland, ME, USA), stained with ethidium bromide, and photographed.

Definition of hypertension

HT was defined as an SBP of ≥140 mmHg or a DBP of ≥90 mmHg, based on referring to "Classification of blood pressure levels, 2014" by the Japanese Society of Hypertension [22]. However, because no information of the use of antihypertensive medication was obtained during the medical examination, we could not consider the influence of such medication when assessing HT in this study. Calculations performed on the statistics of age grade in the National Health and Nutrition Survey in Japan (2004) [23] suggested that 7.4 % of the study participants used antihypertensive medication; we expect this to represent the proportion of the participants who used antihypertensive agents in this study.

Statistical analysis

Results are presented as mean ± standard deviation (SD). Continuous variables were compared using Student's *t* test and categorical variables were compared using the Chi-square test. Moreover, age, BMI, smoking status, and amount of daily alcohol intake were used in a stepwise multiple regression analysis to predict SBP and DBP. If variables were not normally distributed, the statistical analyses were performed after the variables had been log-transformed. All statistical tests were based on two-tailed probability, and $P < 0.05$ was considered to be significant. Statistical analyses were performed using SPSS Ver. 21.

Results

Table 1 presents the characteristics of the study participants (age: 19–64 years; average, 42.6 ± 8.6 years). The proportions of the participants with a current alcohol consumption habit and smoking habit were approximately 54.9 and 57.8 %, respectively. These proportions are around 10 % higher than those measured in the National Health and Nutrition Survey in Japan (2004) [23], according to which the proportions of males aged 20–69 years old who had drinking and smoking habits were 41.1 and 47.4 %, respectively. The genotype frequencies of *ALDH2* polymorphisms were 62.6, 32.7, and 4.7 % for **1/*1*, **1/*2*, and **2/*2*, respectively; these frequencies were approximately the same as those in Japanese men aged 23–64 years old (58.3, 35.6, and 6.1 % for **1/*1*, **1/*2*, and **2/*2*) [6].

The participants' characteristics are presented according to *ALDH2* genetic polymorphisms in Table 2. For the analysis, the heterozygous (**1/*2*) and homozygous (**2/*2*)

Table 1 Characteristics of the participants

Variable	(n = 1,225)
Age (years)	42.6 ± 8.6
Height (cm)	169.3 ± 6.0
Weight (kg)	67.2 ± 9.7
BMI (kg/m^2)	23.4 ± 3.0
SBP (mmHg)	124.3 ± 13.8
DBP (mmHg)	77.6 ± 10.8
AST	24.6 ± 12.1
ALT	31.3 ± 20.6
γ-GTP	64.3 ± 69.5
TC	199.4 ± 35.2
LDL	114.5 ± 33.4
HDL	59.5 ± 14.6
TG	147.9 ± 143.1
Amount of daily alcohol intake (g)	18.1 ± 24.4
Classification of daily alcohol intake (%)	
None	552 (45.1)
6–15 g/day	226 (18.4)
16–32 g/day	222 (18.1)
More than 33 g/day	225 (18.4)
Smoking status (%)	
None	517 (42.2)
1–20 cigarettes/day	571 (46.6)
More than 21 cigarettes/day	137 (11.2)
ALDH2 genetic polymorphism (%)	
**1/*1*	767 (62.6)
**1/*2*	400 (32.7)
**2/*2*	58 (4.7)

Values are mean ± SD, number of the participants

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *WBC* white blood cell, *RBC* red blood cell, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *γ-GTP* γ-glutamyl transpeptidase, *TC* total cholesterol, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *TG* triglyceride, *ALDH2* aldehyde dehydrogenase 2

genetic polymorphisms of *ALDH2* were combined to enhance statistical power. SBP, DBP, AST, ALT, γ-GTP, TC, HDL, TG, and amount of daily alcohol intake in the **1/*2* or **2/*2* group were significantly lower than their levels in the **1/*1* group. Moreover, significant differences were also observed in the classification of daily alcohol intake, but no significant differences were present in age, height, weight, BMI, LDL, smoking status, and presence of HT.

Age, BMI, smoking status, and amount of daily alcohol intake were used in a stepwise multiple regression analysis to predict SBP and DBP. The prediction models are shown in Table 3, and the analysis was performed separately for *ALDH2* genetic polymorphisms **1/*1* and **1/*2* or **2/*2*. In the case of the *ALDH2* genetic polymorphism **1/*1*, the models of SBP and DBP were statistically significant ($[F\ (2,\ 764) = 80.347,\ P < 0.001]$ and $[F\ (3,\ 763) = 82.554,\ P < 0.001]$, respectively), and accounted for approximately 17 and 24 % of the variance of SBP ($R^2 = 0.174$, adjusted $R^2 = 0.172$) and DBP ($R^2 = 0.245$, adjusted $R^2 = 0.242$). The significant variables were age and BMI in relation to SBP, and age, BMI, and smoking status in relation to DBP. In the case of the *ALDH2* genetic polymorphism **1/*2* or **2/*2*, the models of SBP and DBP were statistically significant ($[F\ (3,\ 454) = 33.847,\ P < 0.001]$ and $[F\ (3,\ 454) = 48.070,\ P < 0.001]$, respectively), and accounted for approximately 18 and 24 % of the variance of SBP ($R^2 = 0.183$, adjusted $R^2 = 0.177$) and DBP ($R^2 = 0.241$, adjusted $R^2 = 0.236$). The significant variables were age, BMI, and amount of daily alcohol intake in relation to SBP, and age, BMI, and smoking status in relation to DBP.

Discussion

ALDH2, *ADH2*, and *CYP2E1* polymorphisms were previously identified to affect alcohol metabolism [11]. Among various genetic polymorphisms, *ALDH2* polymorphisms

Table 2 Characteristics of the participants stratified according to the *ALDH2* genetic polymorphism

	**1/*1* ($n = 767$)	**1/*2* or **2/*2* ($n = 458$)	*P* value
Age (years)	42.5 ± 8.7	42.7 ± 8.4	0.681
Height (cm)	169.4 ± 5.9	169.1 ± 6.2	0.344
Weight (kg)	67.6 ± 9.8	66.6 ± 9.5	0.700
BMI (kg/m^2)	23.5 ± 3.0	23.3 ± 2.9	0.116
SBP (mmHg)	125.5 ± 13.7	122.2 ± 13.6	<0.001
DBP (mmHg)	78.6 ± 10.5	76.0 ± 11.0	<0.001
AST[a]	25.9 ± 13.7	22.5 ± 8.6	<0.001
ALT[a]	33.9 ± 22.5	27.1 ± 15.9	<0.001
γ-GTP[a]	75.2 ± 81.0	46.1 ± 37.8	<0.001
TC[a]	201.8 ± 35.5	195.5 ± 34.4	0.002
LDL[a]	114.2 ± 34.7	115.1 ± 31.3	0.632
HDL[a]	61.0 ± 14.7	56.9 ± 14.0	<0.001
TG[a]	153.4 ± 152.5	138.8 ± 125.4	0.046
Amount of daily alcohol intake (g)	19.6 ± 25.5	15.6 ± 22.4	0.004
Classification of daily alcohol intake (%)			0.019
None	324 (42.2)	228 (49.8)	
6–15 g/day	139 (18.1)	87 (19.0)	
16–32 g/day	147 (19.2)	75 (16.4)	
More than 33 g/day	157 (20.5)	68 (14.8)	
Smoking status (%)			0.589
None	322 (42.0)	195 (42.6)	
1–20 cigarettes/day	364 (47.5)	207 (45.2)	
More than 21 cigarettes/day	81 (10.6)	56 (12.2)	
Presence of HT (%)			0.055
Control group	630 (82.1)	396 (86.5)	
HT group	137 (17.9)	62 (13.5)	

Values are mean ± SD, number of the participants

Data were analyzed by Student's *t* test and Chi-square test

[a] Log transformed when testing differences between ALDH2 genetic polymorphism

Table 3 Summary of multiple regression analysis for blood pressure by *ALDH2* genetic polymorphism

Objective variables	Selected explanatory variables	β	SE	P value	Adjusted R^2
*ALDH2 *1/*1* ($n = 767$)					
SBP	Age	0.328	0.052	<0.001	0.172[*,a]
	BMI	0.256	0.151	<0.001	
DBP	Age	0.363	0.038	<0.001	0.242[*,b]
	BMI	0.314	0.111	<0.001	
	Smoking status	−0.079	0.510	0.013	
*ALDH2 *1/*2* or **2/*2* ($n = 458$)					
SBP	Age	0.274	0.070	<0.001	0.177[*,c]
	BMI	0.275	0.200	<0.001	
	Amount of daily alcohol intake	0.084	0.026	0.047	
DBP	Age	0.294	0.055	<0.001	0.236[*,d]
	BMI	0.322	0.156	<0.001	
	Smoking status	−0.118	0.668	0.004	

* $P < 0.001$. Using the stepwise method. β standardized coefficient, *SE* standard error

[a] Multiple regression model adjusted for smoking status, amount of daily alcohol intake

[b] Multiple regression model adjusted for amount of daily alcohol intake

[c] Multiple regression model adjusted for smoking status

[d] Multiple regression model adjusted for amount of daily alcohol intake

have been suggested to be most strongly related to alcohol metabolism. According to a genome-wide association study on blood pressure in East Asians [24], one of the most prominent blood pressure associations was detected on the *ALDH2* locus. Furthermore, Nakagawa et al. [25] reported that alcohol intake dose-dependently increases the risk of HT and elevates SBP and DBP to a considerably greater extent in *ALDH2*2* allele carriers than in non-carriers.

In this study, SBP and DBP were significantly higher in participants who harbored the *ALDH2* genetic polymorphism **1/*1* than in those who harbored the *ALDH2* genetic polymorphism **1/*2* or **2/*2*. Takagi et al. [12] assessed the significance of the effect of the *ALDH2* genotype on blood pressure in Japanese by using a large cohort of 4,000 participants. The *ALDH2* genetic polymorphism **1/*1* was found to be a risk factor for HT in Japanese men mainly through its association with the level of alcohol consumption. Moreover, the sensitivity to the pressor effects of alcohol did not differ according to the *ALDH2* genotype. Our results partially support the conclusion of this previous study. However, we found that the effects of daily alcohol intake differed according to the *ALDH2* genotype.

A lack of ALDH2 activity increases the levels of acetaldehyde and other reactive aldehydes, and induces oxidative stress because mitochondrial ALDH2 reduces the reactive oxygen species formation related to toxic aldehydes that occurs even after light alcohol intake [26, 27]. Oxidative stress increases the risk of various types of pathophysiology, such as HT, Alzheimer's disease, myocardial infarction, coronary spastic angina, colorectal cancer, diabetic retinopathy, and bone marrow failure in Fanconi anemia patients among East Asians [28–34].

In chronic alcohol drinkers, the elevation of acetaldehyde levels results in an increase in angiotensin I levels, an effect that might enhance the activity of the renin–angiotensin system cascade and, consequently, contribute to HT [35, 36]. Acetaldehyde-mediated inhibition of angiotensin-converting enzyme activity could be responsible for transient acute vasodilation and facial flushing in response to alcohol [37]. People who harbor the *ALDH2* genetic polymorphism **1/*2* or **2/*2* refrain from excessive alcohol consumption because of the aversive reactions that result from increased acetaldehyde levels. Therefore, the *ALDH2*2* allele strongly affects drinking behavior [16, 17, 38]. Takeshita et al. [13] reported that daily alcohol consumption increased significantly in the following order of *ALDH2* polymorphisms: **2/*2*, **1/*2*, **1/*1*. In this study, the amount of daily alcohol intake and the classification of daily alcohol intake were found to differ in a statistically significant manner according to the *ALDH2* genetic polymorphisms. These results suggest that people who harbor the *ALDH2*2* allele either develop alcohol tolerance because enzymes other than ALDH2 also function in alcohol metabolism, or drink alcohol and experience unpleasant intoxication symptoms such as headache, nausea, palpitation, and facial flushing. These findings could be partly attributed to the Japanese drinking culture, which is characterized by a high social tolerance for alcohol

consumption and is reflected in the widespread belief in Japan that drinking facilitates socialization and mutual understanding between people [39, 40].

In this study, we found that AST, ALT, γ-GTP, TC, HDL, TG, and amount of daily alcohol intake were significantly higher in the *ALDH2 *1/*1* group than in the *ALDH2 *1/*2* or **2/*2* group. Alcohol consumption is widely recognized to increase the HDL cholesterol level. The precise mechanism through which HDL levels are elevated in response to alcohol consumption remains unclear, but alcohol has been postulated to affect HDL cholesterol metabolism through the ethanol-oxidizing system, which is distinct from the *ALDH* cascade [41, 42]. Gaziano et al. [43] reported that alcohol consumption was associated with increased levels of HDL, and that HDL was associated with a diminished risk of myocardial infarction. Moreover, Husemoen et al. [44] reported that alcohol drinking exerted beneficial effects on HDL levels, but also that blood pressure, TG, TC, and LDL were elevated in heavy/excessive drinkers.

Takeshita et al. [45] reported that activities of liver-function biomarkers (AST and ALT) were considerably higher in the *ALDH2 *1/*1* group than in the *ALDH2 *1/*2* group among moderate and heavy drinkers. The study also suggested that alcohol drinking differentially affected AST and ALT in the two *ALDH2* genotype groups. Takeshita and colleagues further suggested that their findings might also be partly relevant to the anti-inflammation effects of acetaldehyde, because increased concentrations of acetaldehyde in the *ALDH2 *1/*2* group might lead to an increased production of prostaglandins, which would result in vasodilation and an improvement of microcirculation in target tissues. In accord with this previous study, we suggest that the influence of alcohol consumption is manifested in the form of elevated activities of liver-function biomarkers and increased levels of blood lipids in the *ALDH2 *1/*1* group; however, we have not identified the specific values of these measurements at which immediate medical problems are caused.

This study was conducted to investigate how *ALDH2* genetic polymorphism and alcohol intake affect the onset of high blood pressure. As shown by the results of multiple regression analysis (stepwise method; Table 3), the predictive models of SBP and DBP were confirmed to vary according to *ALDH2* polymorphisms. The explanatory (independent) variables age and BMI were strongly weighted in all models. In the case of the *ALDH2* genetic polymorphism **1/*2* or **2/*2*, we found a weak but statistically significant effect of amount of daily alcohol intake (an explanatory (independent) variable) on SBP. These findings suggest that the strength of the influence of daily alcohol intake varies depending on the *ALDH2* genetic polymorphism.

Genetic polymorphism of *ALDH2* in humans results in altered pharmacokinetic properties and metabolism of ethanol, which leads to the accumulation of the ethanol metabolite acetaldehyde following alcohol intake. Acetaldehyde accumulation is considered to be responsible for the unfavorable effects produced by *ALDH2* variants. The presence of mutant or inactive *ALDH2*2* commonly leads to increased HT risk in humans. This association between blood pressure and ALDH2 enzymatic activity might be affected by the interplay between genetic and environment factors, such as lifestyle and ethnicity.

The findings of our study provide crucial information that could help prevent alcohol-induced HT that involves distinct levels of risk posed by *ALDH2* genetic polymorphism. Moreover, our findings will also assist in the practical implementation of health education among East Asians who consume alcohol. The genetic polymorphism of *ALDH2* affects the level of risk of various alcohol-related problems, including high blood pressure.

Nakamura et al. [46] have suggested that a moderation of alcohol intake is not adequate for reducing the prevalence of HT in the Japanese population; this was based on an examination of NIPPON DATA90 (data from the Fourth National Survey on Circulatory Disorders, Japan, in 1990). *ALDH2* genetic polymorphism—the missense mutation in *ALDH2* (*ALDH2*2* allele)—is common in East Asians, but it does not occur among Caucasians [47]. Therefore, alcohol consumption plays a critical role in the high prevalence of HT in the Japanese population. However, the general public cannot readily obtain exact information regarding their genotypes; in this context, two available tests are noteworthy.

First, Yokoyama et al. [48] have invented a simple questionnaire on facial flushing for identifying the occurrence of inactive *ALDH2* without defining the alcohol dose; the questionnaire contains two questions: (a) do you have a tendency to flush in the face immediately after drinking a glass (180 mL) of beer? (b) Did you have a tendency to flush in the face immediately after drinking a glass of beer during the first to second year after you started drinking? The sensitivity and specificity of these question are both approximately 90 % in the case of Japanese people aged 40 years and older regardless of their sex. The use of this questionnaire should facilitate the assessment of the *ALDH2* genotype in the general public. Second, *ALDH2* is expressed throughout the body, including in the skin, and skin-patched alcohol (ethanol) is converted into acetaldehyde. Thus, the alcohol (ethanol) patch test has been shown to serve as a useful tool for checking for the presence of an *ALDH2*2* mutation [49].

People who exhibit a weak ability to consume alcohol or become easily drunk but still consume large amounts of alcohol must pay attention to liver function and HT.

Therefore, determining beforehand the *ALDH2* genotype can help prevent several alcohol-related problems.

The limitations of our study are the following. First, no questionnaire was used to assess the use of antihypertensive medication. Second, the presented statistics were based on the self-reported amount of daily alcohol intake. Participants with the **1/*1* genotype might have reported an amount less than the genuine intake, and a possible low sensitivity to the pressor effects of alcohol in these participants might be masked by this inaccurate underestimation. However, participants who had recently stopped drinking alcohol were excluded from the analyses, and therefore it is unlikely that this potential source of bias exerted any effect on our results. Third, for the purpose of this study, we combined the heterozygous (**1/*2*) and homozygous (**2/*2*) genetic polymorphisms of *ALDH2*. Because the *ALDH2 *2/*2* sample size was small, the statistical power was low when the participants were divided into three groups according to the *ALDH2* genotypes. We found a weak but statistically significant correlation between daily alcohol intake and SBP in the case of the *ALDH2* genetic polymorphism **1/*2* or **2/*2*, but additional Japanese participants are required to clearly demonstrate this in the future. Lastly, we also determined that smoking status was associated with both *ALDH2* genetic polymorphisms, **1/*1** and *1/*2* or **2/*2*, but this result must be further verified.

The aforementioned potential error in self-reported alcohol amounts might not be adequately large to alter our findings. Thus, in any public health measure employed to prevent HT, attention must be paid to alcohol consumption in association with the *ALDH2* genetic polymorphism.

In summary, our results have demonstrated that the interaction between alcohol intake and *ALDH2* genetic polymorphism might affect systolic blood pressure in adult male workers.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflicts of interest exist.

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