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Alcohol and aldehyde dehydrogenase polymorphisms and risk for suicide: a preliminary observation in the Japanese male population

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Epidemiological studies have shown that excessive alcohol consumption is a potent risk factor to develop suicidal behavior. Genetic factors for suicidal behavior have been observed in family, twin, and adoption studies. Because alcohol dehydrogenase (*ADH1B*) His47Arg and mitochondrial aldehyde dehydrogenase (*ALDH2*) Glu487Lys single nucleotide polymorphisms (SNPs), which affect alcohol metabolism, have been reported to exert significant impacts on alcohol consumption and on the risk for alcoholism in East Asia populations, we explored associations of the two functional SNPs with suicide using a case–control study of 283 completed suicides and 319 control subjects in the Japanese population. We found that the inactive *ALDH2* allele (487Lys) was significantly less frequent in the completed suicides (19.3%) than in the controls (29.3%), especially in males, whereas this was not the case in females. The males bearing alcoholism-susceptible homozygotes at both loci (inactive *ADH1B* Arg/Arg and active *ALDH2* Glu/Glu genotypes) have a 10 times greater risk for suicide compared with the males bearing alcoholism-protective homozygotes at both loci. Our data show the genetic impact of the two polymorphisms on suicidal behavior in the Japanese population, especially in males. Because we did not verify the daily alcohol consumption, the association of these SNPs with suicide might be due to alcoholism itself. Further studies using case–control subjects, which verifies the details of current and past alcohol consumption and diagnosis for alcoholism, are required to confirm these findings.

Keywords: ADH1B, alcohol dehydrogenase, ALDH2, association study, mitochondrial aldehyde dehydrogenase, polymorphism, suicide

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Suicide is a major public health problem worldwide, in which higher rates of above 20 per 100 000 are seen in East Asia countries such as China, Japan, and the Republic of Korea (http://www.who.int/mental_health/resources/suicide/en/index.html). Suicide is not simply a response to stress, but generally a complex of psychiatric disorders. Even though over 90% of suicide victims (SV) or suicide attempters have a diagnosable psychiatric illness, most patients never attempt suicide, indicating a predisposition to suicidal behavior that is independent of the main psychiatric disorder (Mann 2003). Genetic factors for suicide have been also observed in family, twin, and adoption studies (Roy *et al*. 1997) and completed suicides are thought to be more homogeneous than suicide attempters in terms of inheritance of suicidal behavior (Brent & Mann 2005).

Heavy alcohol consumption is among the well-known risk factors for suicide (Mann 2002). The World Health Organization reported that about 17.6% of all suicides are estimated to occur in relation to alcohol-related disorders, and the lifetime suicide rate is estimated to be 7% among those who misuse alcohol (Inskip *et al*. 1998). In addition, acute alcohol use impairs judgment, reality testing, and diminishes responsibility, resulting in raising the risk for attempted and completed suicide (Sher *et al*. 2009). It has been known that there exist racial differences in alcohol metabolism that appear to be substantially influenced by genetic factors.

Alcohol metabolism occurs in two major steps: oxidation of alcohol to acetaldehyde by the alcohol dehydrogenase enzymes, especially by *ADH1B*, and further oxidation of acetaldehyde into acetate by aldehyde dehydrogenase enzymes, mainly *ALDH2*. Single nucleotide polymorphisms (SNPs) of the two enzymes' gene loci, *ADH1B* His47Arg (rs1229984) and *ALDH2* Glu487Lys (rs671) SNPs, which affect alcohol metabolism, have been reported to exert significant impacts on alcohol consumption and on the risk for alcoholism in East Asia populations (Higuchi *et al*. 1996; Kim *et al*. 2008). The *ALDH2* 487Lys allele encodes a catalytically inactive subunit which allows high levels of acetaldehyde to accumulate in the blood, resulting in alcohol-related adverse reactions, such as flushing, palpitation, nausea, headache, drowsiness, breathlessness, and general discomfort. The *ALDH2* 487Lys allele is best known for protection against alcoholism and is essentially absent

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in all parts of the world except East Asia populations. The frequency of 487Lys allele was significantly less in alcoholism (0.02–0.07) than in general East Asia populations (0.20–0.30) (Li *et al*. 2009). The *ADH1B* 47His allele encodes the active isoform which represents a much higher activity of the usual form with 47Arg allele, resulting in more rapid acetaldehyde accumulation in the blood than occurs with the usual *ADH1B* isoform (47Arg). The active *ADH1B* allele (47His) was also reported to be protective against alcoholism.

Because chronic and acute excessive consumption of alcohol have been suggested to be involved in the pathogenesis of suicidal behavior, these functional SNPs regulating drinking behavior may also determine the risk of suicidal behavior. We, therefore, conducted a case–control study of 283 completed suicides and 319 control subjects to explore the associations of *ADH1B* His47Arg and *ALDH2* Glu487Lys SNPs with suicide in Japanese.

Materials and methods

The study population consisted of 283 completed suicides (192 males: mean age ± SD, 49.2 ± 16.3 years; 91 females: 47.0 ± 19.2 years) on whom autopsies were conducted at the Department of Legal Medicine, Kobe University Graduate School of Medicine. The definition of suicide was based on the results of medico legal examination and the police investigation as required by Japanese law. All subjects were ethnically Japanese. The characteristics of subjects are shown in Table 1. The methods of suicide were hanging (146), jumping from heights (72), drowning (11), several deep cuts (9), drug overdose (8), gas poisoning (6), jumping in front of a vehicle (4), burning (4), and other methods (23). We were not allowed to conduct a full psychological autopsy by contacting the bereaved family when and after the autopsy because of a local constraint of Ethical Committee for the genetic study. Although accurate information about the clinical backgrounds of the completed suicides could not be obtained, we excluded ones who were reported to be obviously treated for alcoholism from subjects studied here.

The controls consisted of age-matched 319 unrelated volunteers (205 males: mean age ± SD, 46.3 ± 19.6 years; 114 females: 45.6 ± 15.3 years). They were recruited from the main island of Japan, with written informed consent after the purpose and procedures of the study were explained. All were healthy and of Japanese descent, and none of them manifested psychiatric problems in unstructured interviews using the Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria by two psychiatrists.

Peripheral blood was collected from SV and comparison subjects, and leukocyte DNA was purified for genotyping by a standard method. The *ADH1B* His47Arg (rs1229984) and *ALDH2* Glu487Lys (rs671) SNPs were confirmed by the Predesigned Taqman SNP genotyping Assay selected from the Applied Biosystems database (http://www.appliedbiosystems.com).

The Hardy–Weinberg equilibrium and associations between SNPs and suicide were examined with the chi-square test. Fisher's exact test was applied, if necessary. Odds ratio (OR) analyses and Student's *t*-tests were performed with the SPSS software (Version 10.0; SPSS, Chicago, IL, USA). Power analysis was performed with the program PS v2.1.31 (Dupont & Plummer 1998). Statistical significance was defined at $P < 0.05$. Because this study was preliminary and sample size was relatively small, we did not applied corrected *P*-values for multiple comparisons. This study was approved by the Ethical Committee for Genetic Studies of Kobe University Graduate School of Medicine.

Results

The characteristics of subjects are shown in Table 1. We analyzed data separately for gender in this study, because remarkable gender differences in suicide rates are observed worldwide (about a three times higher in males than in females) and because gender differences in pathogenesis of suicidal behavior are speculated in previous findings (Fukutake *et al*. 2008; Hishimoto *et al*. 2006). No statistically significant differences were observed between completed suicides and controls for the mean values of age in the male and female groups ($t = 0.57$, df = 169.5, $P = 0.57$ and $t = 1.59$, df = 389.3, $P = 0.11$, respectively). Overall distribution of suicide methods was significantly different between the male and female groups ($\chi^2 = 17.7$, df = 8, $P = 0.02$). The frequency of hanging cases in the males (55.2%) appeared higher than in the female (44.0%), although statistically not significant ($\chi^2 = 3.13$, df = 1, $P = 0.07$). The frequency of drowning cases in the females (9.9%)

Table 1: Characteristics of subjects

	Male SV ($n = 192$)	Male controls ($n = 205$)	Female SV ($n = 91$)	Female controls ($n = 114$)
Age ± SD, years	49.2 ± 16.3	46.3 ± 19.6	47.0 ± 19.2	45.6 ± 15.3
Suicide methods (%)*				
Hanging	106 (55.2)	—	40 (44.0)	—
Jumping from heights	46 (24.0)	—	26 (28.6)	—
Drowning†	2 (1.0)	—	9 (9.9)	—
Several deep cuts	6 (3.1)	—	3 (3.3)	—
Drug overdose	5 (2.6)	—	3 (3.3)	—
Gas poisoning	6 (3.1)	—	0 (0.0)	—
Jumping in front of a vehicle	3 (1.6)	—	1 (1.1)	—
Burning	3 (1.6)	—	1 (1.1)	—
Other methods (include not specified)	15 (7.8)	—	8 (8.8)	—

*The distribution of suicide methods between the male and female groups: $P = 0.02$ (Fisher's exact test).
†The drowning group vs. others between the male and female groups: $P = 0.0008$ (Fisher's exact test).

Table 2: Allelic and genotypic frequencies of the *ALDH2* Glu487Lys (rs671) and *ADH1B* His47Arg (rs1229984) polymorphisms in completed suicides and controls between male and female

	Male SV ($n = 192$)	Male control ($n = 205$)	Odds ratio (95% CI)	Female SV ($n = 91$)	Female control ($n = 114$)	Odds ratio (95% CI)
ALDH2 Glu487Lys (rs671, G-to-A polymorphism)						
GG	125 (65.1)	105 (51.2)	1	47 (51.6)	64 (56.1)	1
GA	60 (31.3)	80 (39.0)	0.63 (0.41–0.96)	37 (40.7)	41 (36.0)	1.2 (0.69–2.2)
AA	7 (3.6)	20 (9.8)	0.30 (0.12–0.72)	7 (7.7)	9 (7.9)	1.1 (0.37–3.0)
G	310 (80.7)	290 (70.7)	1	131 (72.0)	169 (74.1)	1
A	74 (19.3)	120 (29.3)	0.58 (0.41–0.80)	51 (28.0)	59 (25.9)	1.1 (0.72–1.7)
ADH1B His47Arg (rs1229984 SNP, A-to-G polymorphism)						
AA	111 (57.8)	128 (62.4)	1	62 (68.1)	63 (55.3)	1
AG	65 (33.9)	69 (33.7)	1.1 (0.71–1.7)	29 (31.9)	40 (35.1)	0.74 (0.41–1.3)
GG	16 (8.3)	8 (3.9)	2.3 (0.95–5.6)	0 (0.0)	11 (9.6)	NA*
A	287 (74.7)	325 (79.3)	1	153 (84.1)	166 (72.8)	1
G	97 (25.3)	85 (20.7)	1.3 (0.93–1.8)	29 (15.9)	62 (27.2)	0.51 (0.31–0.83)

*Not available due to lack of subjects within the categories.

was significantly higher than in the males (1.0%) ($\chi^2 = 12.9$, df = 1, $P = 0.0008$).

Genotype distributions and allele frequencies for the *ADH1B* His47Arg and *ALDH2* Glu487Lys SNPs are shown in Table 2. The genotype distribution of the *ADH1B* His47Arg SNP did not significantly differ from Hardy–Weinberg equilibrium in male suicides ($P = 0.20$), male controls ($P = 0.94$), female suicides ($P = 0.14$), or female controls ($P = 0.30$). Also the genotype distribution of the *ALDH2 Glu487Lys* SNP did not differ from Hardy–Weinberg equilibrium in male suicides ($P = 1.00$), male controls ($P = 0.49$), female suicides ($P = 1.00$), or female controls ($P = 0.63$).

Among the males, both the genotype distribution and allele frequency of *ALDH2* Glu487Lys SNP showed significant differences between the completed suicides and control groups ($\chi^2 = 10.4$, df = 2, $P = 0.0054$ and $\chi^2 = 10.7$, df = 1, $P = 0.0012$, respectively). The alcoholism-protective inactive *ALDH2* allele (487Lys) was significantly less frequent in the completed suicides (19.3%) than in the controls (29.3%). The OR for phenotype was 0.58 [95% confidence intervals (CI): 0.41–0.80]. A dominant model (Glu/Glu vs. Glu/Lys + Lys/Lys) analysis of the *ALDH2* Glu487Lys SNP showed a slight enhanced association with the completed suicide ($\chi^2 = 7.84$, df = 1, $P = 0.0051$, OR = 0.56, 95% CI: 0.38–0.84). By contrast, neither genotype distribution nor allele frequency of the *ADH1B* His47Arg SNP was associated with suicide in the males, while the alcoholism-susceptible usual *ADH1B* allele (47Arg) appeared more frequent in the completed suicides (25.3%) than in the controls (20.7%). Based on observed allele frequency of the *ADH1B* His47Arg and *ALDH2* Glu487Lys SNPs in the males, the current samples yielded a power of 0.19 and 0.64, respectively, for the detection of nominally significant results.

Among the females, neither genotype distribution nor allele frequency of the *ALDH2* Glu487Lys SNP showed significant differences between the completed suicide and control groups ($\chi^2 = 0.484$, df = 2, $P = 0.785$ and $\chi^2 = 0.237$, df = 1, $P = 0.626$, respectively), while both the genotype distribution and allele frequency of *ADH1B* His47Arg SNP showed significant differences between the completed suicide and control groups ($\chi^2 = 10.2$, df = 2, $P = 0.0026$ and $\chi^2 = 7.43$, df = 1, $P = 0.0083$, respectively). Contrary to our expectation, the alcoholism-susceptible usual *ADH1B* allele (47Arg) was significantly less frequent in the completed suicide (15.9%) than the controls (27.2%). The OR for phenotype was 0.51 (95% CI: 0.31–0.83). Based on observed allele frequency of the *ADH1B* His47Arg and *ALDH2* Glu487Lys SNPs in the females, the current samples yielded a power of 0.49 and 0.06, respectively, for the detection of nominally significant results.

Analyses of combination of the *ALDH2* Glu487Lys and *ADH1B* His47Arg SNPs showed more protective risk for suicide in a synergistic manner only among the males (Table 3). Individuals bearing alcoholism-protective homozygotes at both loci (inactive *ALDH2* Lys/Lys genotypes and active *ADH1B* His/His) have about five times smaller risk for suicide [OR: 0.22, 95% CI: 0.06–0.82] compared with a major group individuals bearing homozygous *ALDH2* Glu/Glu and homozygous *ADH1B* His/His genotypes as a reference. In another respect, males bearing alcoholism-susceptible homozygotes at both loci (active *ALDH2* Glu/Glu and usual *ADH1B* Arg/Arg genotypes) have 10 times greater risk for suicide compared with males bearing alcoholism-protective homozygotes at both loci [OR: 10.0, 95% CI: 1.80–55.6]. On the other hand, no synergistic manner between the two polymorphisms was observed in the females (Table 3).

Discussion

To the best of our knowledge, this is a first report to explore the genetic association of *ADH1B* His47Arg and *ALDH2* Glu487Lys SNPs with suicide. The alcoholism-associated *ALDH2* Glu487Lys SNP was also significantly associated with suicide in males, and individuals bearing alcoholism-protective homozygotes at both loci (active *ADH1B* His/His and inactive *ALDH2* Lys/Lys genotypes) have about five

Table 3: Combined genotype of *ALDH2* Glu487Lys and *ADH1B* Arg47His polymorphisms and OR (95% CI) for completed suicides

	ALDH2 Glu487Lys (G-to-A polymorphism)					
	ALDH2 G/G		*ALDH2* G/A		*ALDH2* A/A	
	SV/CT (%)	OR (95% CI)	SV/CT (%)	OR (95% CI)	SV/CT (%)	OR (95% CI)
Male						
ADH1B His47Arg (A-to-G polymorphism)						
ADH1B A/A	74 (38.5)/66 (32.2)	1.0 (reference)	34 (17.7)/50 (24.3)	0.61 (0.35–1.05)	3 (1.6)/12 (5.9)	0.22 (0.06–0.82)*
ADH1B A/G	41 (21.4)/35 (17.1)	1.04 (0.60–1.83)	20 (10.4)/28 (13.7)	0.63 (0.33–1.23)	4 (2.1)/6 (2.9)	0.59 (0.16–2.20)
ADH1B G/G	10 (5.2)/4 (2.0)	2.22 (0.67–7.45)	6 (3.1)/2 (1.0)	2.68 (0.52–13.7)	0 (0.0)/2 (1.0)	NA†
Female						
ADH1B His47Arg (A-to-G polymorphism)						
ADH1B A/A	28 (30.8)/36 (31.6)	1.0 (reference)	28 (30.8)/21 (18.4)	1.71 (0.81–3.63)	6 (6.6)/6 (5.3)	1.29 (0.37–4.42)
ADH1B A/G	19 (20.9)/21 (18.4)	1.16 (0.53–2.57)	9 (9.9)/18 (15.8)	0.64 (0.25–1.65)	1 (1.1)/3 (2.6)	0.43 (0.04–4.35)
ADH1B G/G	0 (0.0)/7 (6.1)	NA†	0 (0.0)/4 (3.5)	NA†	0 (0.0)/0 (0.0)	NA†

SV, suicide victims; CT, controls; OR, odds ratio; 95% CI, confidence interval.
†Not available due to lack of subjects within the categories.
*$P < 0.05$.

times smaller risk for suicide, especially in males. In addition, males bearing alcoholism-susceptible homozygotes at both loci (usual *ADH1B* Arg/Arg and active *ALDH2* Glu/Glu genotypes) have 10 times greater risk for suicide compared with males bearing alcoholism-protective homozygotes at both loci.

Our findings imply that individuals who are tolerant of alcohol consumption have a higher rate of completing suicides. This appears to support empirical evidence that excessive alcohol consumption is a potent risk factor for developing suicidal behavior. However, our results should be carefully interpreted. First of all, neither the completed suicides nor control subjects in this study were accurately evaluated for daily (past and current) alcohol consumption. Although we excluded those who were obviously treated for alcoholism, most alcoholics, and most alcoholic suicides, are not in current treatment. Therefore, it is highly likely that our suicide sample contained alcoholics. We could not rule out the possibility that the association of *ADH1B* His47Arg and *ALDH2* Glu487Lys SNPs with suicide in males is related to alcoholism itself.

Akechi *et al*. (2006) reported a U-shaped association between alcohol consumption and subsequent death by suicide based on a large population-based cohort of Japanese middle-aged males. Non-drinkers and regular drinkers who consumed more than 414 g of ethanol per week had significantly higher risks for suicide than occasional drinkers. Among non-drinkers, ex-drinkers had a significantly higher risk for suicide than occasional drinkers. The findings of this report mean that the risk for suicide in a general population cannot be detected simply by current alcohol habit.

Nevertheless, *ADH1B* His47Arg and *ALDH2* Glu487Ly*s* SNPs may be useful as clinical biomarkers for predicting suicide in East Asian countries. The acute effects of alcohol use, such as impaired judgment and reality testing, have been suggested to be important risk factors for attempted and completed suicide among individuals both with and without alcohol-related disorders. Acute effects of alcohol intoxication act as important proximal risk factors to determine the timing of suicidal behavior by translating the statistical potential of distal risk factors, such as alcoholism, into action (Hufford 2001). High rates of positive blood alcohol concentrations have also repeatedly been found among completed suicides (Brent *et al*. 1987; Hayward *et al*. 1992; Hlady & Middaugh 1988). Because the inactive *ALDH2* allele has an inhibitory effect on excess alcohol consumption, genetic factors based on these polymorphisms may be involved in the pathogenesis of suicide in a manner independent of alcoholism.

We could speculate that depressive patients bearing these alcoholism-susceptible alleles are prone to misuse alcohol, resulting in having a greater risk for suicide. In other words, any psychiatric patients bearing alcoholism-protective homozygotes at both loci (active *ADH1B* His/His and inactive *ALDH2* Lys/Lys genotypes) have a smaller risk for suicide. Even though they have a suicidal idea, they are protected from excess alcohol exposure, resulting in decreasing a risk to commit suicide. If we determine the genotype of *ADH1B* His47Arg and *ALDH2* Glu487Lys SNPs in individuals with a high risk for suicidal behavior such as recent suicide attempters, patients with depression, antisocial personality disorder, drug abuser, and so on, we could alert them about the increased risk for suicide with some evidence and even help them to keep away from habitual drinking, acute excessive alcohol consumption, and developing alcoholism.

On the other hand, a statistically significant association of the *ADH1B* His47Arg SNP, but not the *ALDH2* Glu487Lys SNP, with suicide was observed in females. Unexpectedly, the alcoholism-susceptible usual *ADH1B* allele (47Arg) was significantly less in the completed suicide (15.9%) than the controls (27.2%) in the females, although the frequency of alcoholism-susceptible alleles (inactive *ADH1B* alleles) is expected to be higher in the completed suicides from our findings among the males. Alcohol usage is quite different between males and females in Japan. The proportion of regular drinkers in the general population of Japan was estimated at about 11% for females and 68% for males

(Otani *et al*. 2003). These results suggested that suicidal behavior in female is less influenced by drinking behavior than in males and that the pathophysiology of suicidal behavior may be different between males and females. Because the sample size in this study is quite small, especially in the females, our results should be carefully interpreted.

In conclusion, our data show that the genetic impact of the *ADH1B* His47Arg and *ALDH2* Glu487Lys polymorphisms on suicidal behavior. Among males, presence of the inactive *ALDH2* allele may independently decrease the risk for suicide and a synergistic effect of the two SNPs was evident in males. On the contrary, among females, presence of the usual *ADH1B* allele may independently decrease the risk for suicide and no synergistic effect of the two SNPs was observed. Further studies using case–control subjects, which verifies the detail of current and past alcohol consumption and diagnosis for alcoholism, are required to confirm these findings and extrapolate it to other countries especially in East Asia countries.

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