Genetic variants of alcohol-metabolizing enzymes in Brugada syndrome: Insights into syncope after drinking alcohol

Qi Wu MD1 | Hideki Hayashi MD, PhD1 | Daiki Hira PhD2,3 | Keiko Sonoda MD1,4 | Satoshi Ueshima PhD3 | Seiko Ohno MD, PhD1,4,5 | Takeru Makiyama MD, PhD6 | Tomohiro Terada PhD2 | Toshiya Katsura PhD3 | Katsuyuki Miura MD, PhD5,7 | Minoru Horie MD, PhD1,5

1Department of Cardiovascular Medicine, Shiga University of Medical Science, Ohtsu, Japan
2Department of Pharmacy, Shiga University of Medical Science Hospital, Ohtsu, Japan
3College of Pharmaceutical Sciences, Ritsumeikan University, Kusatsu, Japan
4Department of Bioscience and Genetics, National Cerebral and Cardiovascular Center, Saita, Japan
5Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Ohtsu, Japan
6Department of Cardiovascular and Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
7Department of Public Health, Shiga University of Medical Science, Ohtsu, Japan

Correspondence
Minoru Horie, Department of Cardiovascular Medicine, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan.
Email: horie@belle.shiga-med.ac.jp

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Abstract
Background: Patients with Brugada syndrome (BrS) are known to have arrhythmic events after alcohol drinking and are recommended to avoid its excessive intake. Mechanisms underlying the alcohol-induced cardiac events are however unknown. This study aimed to test the hypothesis whether activity of alcohol-metabolizing enzymes determines fatal arrhythmic events after drinking alcohol.
Methods: A total of 198 Japanese patients with BrS were enrolled in this study. These patients were classified into symptomatic (n = 90) and asymptomatic (n = 108) groups. The former was divided into an alcohol-related group (syncope after alcohol drinking, n = 16) and an alcohol-unrelated group (n = 74). Polymerase chain reaction was performed to determine genetic variants of genes encoding alcohol dehydrogenase 1B (ADH1B) and aldehyde dehydrogenase 2 (ALDH2).
Results: The genotype distribution for ALDH2 was not significantly different between symptomatic and asymptomatic groups and between alcohol-related and alcohol-unrelated groups. The genotype distribution for ADH1B was not significantly different between symptomatic and asymptomatic groups, but the genotype ADH1B His/His was significantly more prevalent in the alcohol-related group than in the alcohol-unrelated group (81.3% vs 50%, P = .023). In multivariate logistic regression analysis, the genotype of ADH1B His/His was independently associated with syncope after alcohol drinking (odds ratio, 5.746; 95% confidence interval, 1.580-28.421; P = .007).
Conclusions: Arrhythmic events after alcohol drinking was associated with enhanced activity of alcohol-metabolizing enzyme ADH1B in our cohort of BrS. Therefore, the lifestyle change to avoid the excessive alcohol intake deserves attention.

Keywords
alcohol, alcohol-metabolizing enzymes, Brugada syndrome, polymorphism, syncope
1 | INTRODUCTION

Brugada syndrome (BrS) is diagnosed as a coved-type ST-segment elevation in the right precordial leads. Patients with BrS develop symptoms including ventricular fibrillation (VF), aborted sudden death, syncope, or nocturnal agonal respiration. Previous reports and consensus guideline have shown that alcohol drinking is associated with occurrence of syncope in BrS. Alcohol taken into a body is metabolized by two enzymes, namely alcohol dehydrogenase 1B (ADH1B) and aldehyde dehydrogenase 2 (ALDH2). Alcohol is metabolized to acetaldehyde by ADH1B and sequentially converted to acetate by ALDH2 (Figure 1). The activity of the two enzymes individually varies depending on genetic variants of the enzymes.

The prevalence of BrS is relatively higher in the Southeast Asian countries including Japan compared to the Western countries. This geographical prevalence of BrS is similar to that of loss-of-function type variants in alcohol-metabolizing enzymes: ADH1B and ALDH2, which are more common in Asians than in Caucasians.

More recently, Watanabe et al reported that habitual excessive alcohol drinkers among Japanese BrS patients with implantable cardioverter-defibrillator (ICD) implantation have more fatal arrhythmic events. Therefore, we hypothesized that genetic polymorphisms of the alcohol-metabolizing enzymes would be associated with arrhythmic events in BrS, thus contributing to the pathophysiology and arrhythmogenesis of the disease. The purpose of this study was to test this hypothesis.

2 | METHODS

2.1 | Study population (Figure 2)

The study subjects consisted of 198 BrS Japanese patients (176 men with a mean age of 44.9 ± 15.8 years and 22 women with a mean age of 47.4 ± 17.6 years). The diagnosis of BrS was made on the basis of electrocardiogram (ECG) findings according to the expert consensus statement. In 198 patients, 90 patients (45.5%; 85 men, mean 43.1 ± 15.2 years; 5 women, mean 39.8 ± 19.1 years) had history of syncope and/or aborted sudden cardiac death caused by ventricular tachycardia or fibrillation (symptomatic group). According to medical records, after other causes of syncope like neutrally mediated syncope had been excluded, all the symptomatic patients were thought to have “arrhythmic syncope.” When fatal arrhythmias were recorded by ECG, they were either transient VT/VF or cardiopulmonary arrest due to continued VF. In contrast, remaining 108 patients (54.5%; 91 men, mean 46.5 ± 16.3 years; 17 women, mean 49.7 ± 17.2 years) did not have any episodes of syncope (asymptomatic group) (Figure 2).

The patients of the symptomatic group were further classified into two groups: 16 patients (all men, mean 46.8 ± 13.3 years) who suffered from syncope after drinking alcohol (alcohol-related group) and 74 patients (69 men, mean 42.3 ± 15.5 years; 5 women, mean 39.8 ± 19.1 years) who had no history of syncope after drinking alcohol (alcohol-unrelated group) (Figure 2). Syncope after alcohol drinking is defined as follows: syncope occurred within 6 hours after alcohol drinking, and the amount of drinking alcohol was not specified. Whether or not family history of sudden death was present was evaluated in all patients enrolled in this study. Family history was defined as at least one first-degree family member had died suddenly with a type 1 Brugada ECG pattern during their ante mortem or before the age of 45 years in the absence of known heart disease.

The study was approved by the ethics committee of Shiga University of Medical Science (approval number: 27-161), and written informed consent was obtained from each patient.

2.2 | Determination of ADH1B and ALDH2 genotypes

Genomic DNA was extracted from blood lymphocyte as previously reported. Subsequently, genotyping was performed using TaqMan single-nucleotide polymorphism (SNP) genotyping assay (Applied Biosystems) in a real-time PCR system (StepOnePlus™; Applied Biosystems) for ADH1B (His48Arg; rs1229984) and ALDH2 (Glu504Lys; rs671). Amplification conditions were 95°C for 20 seconds, 40 cycles of 95°C for 3 seconds, and 60°C for 20 seconds. The genotyping was performed with a blind method to the identification of the study subjects.

2.3 | Statistical analysis

The baseline clinical data were expressed as the mean ± standard deviation for continuous variables. A comparison between two groups...
was performed with Student’s t test or the nonparametric Mann-Whitney’s U test, as appropriate. For discrete variables, the data were expressed as counts and percentages. Categorical variables were compared with chi-squared test. Allele frequencies determined by direct gene counting and genotype distributions were checked for departure from Hardy-Weinberg equilibrium using the Pearson’s chi-squared test. A two-tailed value of \( P < .05 \) was considered to be statistically significant. A multiple logistic regression analysis was performed to determine the risk factors of syncope after drinking alcohol. Independent variables were included on the basis of theoretical and clinical grounds. Data analyses were conducted using JMP® 10 (SAS Institute Inc.).

3  | RESULTS

3.1  | Characteristics of the study patients

Table 1A shows the comparison of the clinical characteristics between symptomatic and asymptomatic groups. There was no significant difference in age, family history of sudden death, the frequency of spontaneous type1 Brugada ECG pattern, aborted sudden death, documented VT/VF, VF induced by electrophysiology study, and ICD implantation between the two groups. Based on ICD follow-up, although statistically not significant, VF recurrence rate was higher in the alcohol-related group (25% vs 6.5%, \( P = .096 \)). Indeed, one of our cases experienced appropriate ICD therapy for four episodes of recurrent VF, which were all associated with alcohol drinking. In this group, average time interval between the start of drinking and cardiac events was 3.5 hours.

3.2  | Genotype distribution of ADH1B and ALDH2

Table 2A shows distribution of genotypes for ADH1B and ALDH2 in the symptomatic and the asymptomatic groups. A vast majority of the study patients had the variant ADH1B His genotype (ADH1B Arg/His or ADH1B His/His) and the variant ALDH2 Glu genotype (ALDH2 Glu/Glu or ALDH2 Glu/Lys) in both groups (ADH1B His: 92.3% vs 95.4%, \( P = .355 \); ALDH2 Glu: 91.1% vs 93.5%, \( P = .524 \)). The genotype distributions of the two genes did not deviate from the Hardy-Weinberg equilibrium: ADH1B gene, \( \chi^2 = 0.223, P = .64 \) for the symptomatic group and \( \chi^2 = 1.029, P = .31 \) for the asymptomatic group; ALDH2 genes, \( \chi^2 = 3.324, P = .07 \) for the symptomatic group and \( \chi^2 = 0.017, P = .90 \) for the asymptomatic group. There was no significant overall difference in genotype distribution for ADH1B and ALDH2 in the two groups (ADH1B: \( \chi^2 = 1.013, P = .564 \), Figure 3A; ALDH2: \( \chi^2 = 2.065, P = .379 \), Figure 3B).

Table 2B shows distribution of genotypes for ADH1B and ALDH2 in the alcohol-related syncope group and the alcohol-unrelated group. A vast majority of the study patients had the variant ADH1B His genotype and the ALDH2 Glu genotype in both groups (ADH1B His: 93.8% vs 91.9%, \( P = .801 \); ALDH2 Glu: 93.8% vs 90.6%, \( P = .683 \)). The genotype distribution of the two genes did not deviate from the Hardy-Weinberg equilibrium: ADH1B gene, \( \chi^2 = 2.939, P = .09 \) for the alcohol-related group and \( \chi^2 = 0.019, P = .89 \) for the alcohol-unrelated group; ALDH2 gene, \( \chi^2 = 0.118, P = .73 \) for the alcohol-related group and \( \chi^2 = 3.394, P = .07 \) for the alcohol-unrelated group. There was no significant overall difference in genotype distribution for ADH1B and ALDH2 between the two groups (ADH1B: \( \chi^2 = 2.547, P = .655 \), Figure 4A; ALDH2: \( \chi^2 = 0.190, P = .301 \), Figure 4B).

The prevalence of ADH1B His/His was significantly higher in the alcohol-related group than in the alcohol-unrelated group (81.3% vs 50%, \( P = .023 \)). When compared to those carrying ADH1B Arg/His or ADH1B Arg/Arg (Figure 5), frequency of alcoholic-related syncope was significantly higher in ADH1B His/His (26% vs 7.5%; odds ratio, 4.330; 95% confidence interval, 1.140–16.475; \( P = .023 \)).
### Table 1 Comparison of clinical characteristics

#### A. Symptomatic group vs asymptomatic group

| Variables                        | Symptomatic group (n = 90) | Asymptomatic group (n = 108) | P-value |
|----------------------------------|-----------------------------|------------------------------|--------|
| Age (years)                      | 42.6 ± 15.3                 | 47.0 ± 16.4                  | .077   |
| Male gender, n (%)               | 85 (94.4)                   | 91 (84.3)                    | .023   |
| FH of SD, n (%)                  | 9 (10)                      | 10 (9.3)                     | .860   |
| Spontaneous of type 1 ECG, n (%) | 50 (55.6)                   | 46 (42.6)                    | .069   |

#### B. Alcohol-related group vs alcohol-unrelated group

| Variables                        | Alcohol-related group (n = 16) | Alcohol-unrelated group (n = 74) | P-value |
|----------------------------------|--------------------------------|---------------------------------|--------|
| Age (years)                      | 46.8 ± 13.3                    | 42.1 ± 15.7                    | .275   |
| Male gender, n (%)               | 16 (100)                      | 69 (93.2)                      | .285   |
| FH of SD, n (%)                  | 0 (0)                         | 9 (12.2)                       | .141   |
| Spontaneous of type 1 ECG, n (%) | 10 (62.5)                     | 40 (54.1)                      | .538   |
| Arrhythmia Syncope               | 16 (100)                      | 74 (100)                       | —      |
| Aborted sudden death             | 0 (0)                         | 2 (2.7)                        | .506   |
| Documented VF                    | 7 (43.75)                     | 34 (45.95)                     | .973   |
| VF induced by EPS                | 2 (12.5)                      | 15 (20.27)                     | .472   |
| ICD                              | 8 (50)                        | 46 (62.2)                      | .368   |
| Appropriate shock deliveries     | 2/8 (25)                      | 3/46 (6.5)                     | .096   |

Note: Data are expressed as mean ± standard deviation or n (%). Abbreviations: FH, family history; EPS, electrophysiologic study; ICD, implantable cardioverter defibrillator; SD, sudden death; VF, ventricular fibrillation.

### Table 2 Frequency distribution of genotypes for ADH1B and ALDH2

#### A. Symptomatic group vs asymptomatic group

| Variables               | Symptomatic group (n = 90) | Asymptomatic group (n = 108) | P-value |
|-------------------------|-----------------------------|------------------------------|--------|
| ADH1B gene              |                             |                              |        |
| ADH1B Arg/Arg, n (%)    | 7 (7.8)                     | 5 (4.6)                      | .355   |
| ADH1B Arg/His, n (%)    | 33 (36.7)                   | 45 (41.7)                    | .473   |
| ADH1B His/His, n (%)    | 50 (55.6)                   | 58 (53.7)                    | .794   |
| ALDH2 gene              |                             |                              |        |
| ALDH2 Glu/Glu, n (%)    | 56 (62.2)                   | 59 (54.6)                    | .281   |
| ALDH2 Glu/Lys, n (%)    | 26 (28.9)                   | 42 (38.9)                    | .140   |
| ALDH2 Lys/Lys, n (%)    | 8 (8.9)                     | 7 (6.5)                      | .524   |

#### B. Alcohol-related group vs alcohol-unrelated group

| Variables               | Alcohol-related group (n = 16) | Alcohol-unrelated group (n = 74) | P-value |
|-------------------------|--------------------------------|---------------------------------|--------|
| ADH1B gene              |                               |                                 |        |
| ADH1B Arg/Arg or ADH1B Arg/His, n (%) | 3 (18.8) | 37 (50.0) | .023   |
| ADH1B His/His, n (%)    | 13 (81.2)                     | 37 (50.0)                      |        |
| ALDH2 gene              |                               |                                 |        |
| ALDH2 Glu/Glu, n (%)    | 10 (62.5)                     | 46 (62.2)                      | .980   |
| ALDH2 Glu/Lys, n (%)    | 5 (31.3)                      | 21 (28.4)                      | .818   |
| ALDH2 Lys/Lys, n (%)    | 1 (6.3)                       | 7 (9.5)                        | .683   |

Note: Data are expressed as number (%).
Multivariate regression logistic analysis revealed that the genotype of \textit{ADH1B} His/His was significantly and independently associated with syncope after drinking alcohol, after adjustment for age, \textit{ADH1B} His/His genotypes, spontaneous type1 Brugada ECG pattern (\textit{ADH1B} His/His gene, odds ratio, 5.746; 95\% confidence interval, 1.580-28.421; \( P = .007 \); Table 3). Because patients in the alcohol-related group were all male and did not have family history of sudden death, both gender and family history were not included as the confounding factors.
TABLE 3 Multivariate logistic regression analysis for syncope after drinking alcohol

| Variable                  | OR    | P > |z|   | 95% CI    |
|---------------------------|-------|-----|-----|-----------|
| Age                       | 0.109 | .141| 0.004-2.046 |
| ADH1B His/His             | 5.746 | .007| 1.580-28.421 |
| Spontaneous of type1 ECG  | 0.579 | .357| 0.169-1.840 |

Abbreviations: CI, confidence interval; OR, odds ratio.

4 | DISCUSSION

The present study found: (a) ~20% of fatal arrhythmic events were related to alcohol drinking in our cohort of symptomatic BrS, (b) the distribution for ALDH2 genotypes was not significantly different between symptomatic and asymptomatic groups or between alcohol-related and alcohol-unrelated syncope groups, (c) the distribution for ADH1B genotypes was not significantly different between symptomatic and asymptomatic groups, but the genotype ADH1B His/His was significantly more frequent in the alcohol-related group compared to the alcohol-unrelated group, and (d) the genotype ADH1B His/His was independently associated with syncope after drinking alcohol (Table 3).

Alcohol (ethanol) exerts various physiological responses (Figure 1).11 It is metabolized by two enzymes, namely ADH1B and ALDH2. The former metabolizes ethanol to acetaldehyde in the cytosol; the latter acetaldehyde to acetic acid in the mitochondria. The ADH1B gene is located on chromosome 4, and its single-nucleotide polymorphism (SNP: rs1229984) replaces arginine to histidine at residue 47 (Arg47His). The ALDH2 on chromosome 12 has also a SNP (rs671) which substitutes glutamate with lysine at position 504 (Glu504Lys). These two SNPs exert loss-of-function effects and are more common in East Asians than in Caucasians and play essential roles in alcohol-induced physical reactions.11-13

The variant ADH1B His/His is a super-active subunit of ADH1B and possesses ~40 times more efficient ethanol metabolizing activity compared to ADH1B Arg/Arg.11,14 and is seen in 60% of Japanese.15,16 In contrast, 57% of Japanese are homozygous for the ALDH2 Lys/Lys which has normal enzymatic activity. Homozygotes WU et al.

Among Japanese BrS patients implanted with ICD, Watanabe et al9 reported that habitual excessive alcohol drinkers showed significantly more frequent recurrence of fatal arrhythmic events. Because carriers with ADH1B His/His have stronger ability of alcohol metabolism and higher level of alcohol consumption,11,18 their report may suggest the same results as our findings in that the ADH1B His/His genotype was significantly more frequent among the patients suffering alcohol-related fatal arrhythmic events. Our results also support the recommendation of 2014 Expert Consensus Statement1 to avoid the excessive alcohol intake to prevent the arrhythmic risk as a lifestyle change.

The super-active ADH1B variant results in an earlier and higher peak of blood acetaldehyde level. Acetaldehyde then stimulates the sympathetic nervous tone through the release of catecholamine from sympathetic nervous terminals.19,20 The patients carrying this SNP might have an earlier and larger increase in sympathetic tone than those with other SNP carriers. On cessation of ethanol drinking, the larger sympathetic stimulation declines with disappearance of acetaldehyde, and the following stronger parasymptomatic activation could be possible to occur. The strongest alcohol metabolizers may have a large meal concurrently with a large amount of alcohol consumption, producing a full stomach condition. It is well known that, a full stomach test can unmask type1 ECG by through the increased vagal activity.21

It is well known that autonomic function influences the severity of BrS.22-25 Both experimental and clinical studies have shown that ST-segment elevation, a marker of increased risk of arrhythmic events, is mitigated by the administration of beta-adrenergic agonists and enhanced by parasymptomatic agonists.26,27 In this connection, Makimoto et al28 reported that 34 out of 93 patients with BrS showed significant ST segment elevation in V1 to V3 leads during the recovery phase after exercise tolerance test, indicating the involvement of parasymptomatic reactivation. In these 34 patients, clinical prognosis was significantly worse and SCN5A mutations were more frequently identified.

There are several reports on excessive alcohol consumption and increased risk of sudden cardiac death.29,30 In an experimental study, excessive alcohol directly exerts proarrhythmic effects by inhibiting sodium and calcium channels.31,32
4.1 | Limitations

Although it is known that alcohol-induced flushing and frequency of habitual drinking are useful information to learn if a subject tolerates alcohol intake, the medical record was not available. The ethnicity-dependent difference of frequency of alcohol-related syncpe in BrS remains unknown because our study population was limited to the Japanese.

5 | CONCLUSION

Arrhythmic events after alcohol drinking in BrS patients were associated with enhanced activity of alcohol-metabolizing enzyme caused by ADH1B His/His, supporting the recommendation of 2014 Expert Consensus Statement in that the excessive alcohol intake should be avoided.1

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CONFLICTS OF INTEREST

Authors declare no conflict of interests for this article.

ORCID

Qi Wu https://orcid.org/0000-0001-9212-4139
Seiko Ohno https://orcid.org/0000-0003-1209-8896
Minoru Horie https://orcid.org/0000-0002-9029-2339

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