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Original Article

Genetic screening of *KCNJ8* in Japanese patients with J-wave syndromes or idiopathic ventricular fibrillation ☆

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ABSTRACT

Background: J-point elevation has been demonstrated to be associated with ventricular fibrillation (VF) and has been proposed as a cause of the J-wave syndrome (JWS). A mutation of *KCNJ8*, S422L, was reported as a culprit gene. This study aimed to determine the prevalence of *KCNJ8* mutations in a Japanese population with JWS or idiopathic VF (IVF).

Methods: A total of 230 probands with JWS and IVF underwent genetic screening of *KCNJ8*. To analyze and compare clinical and electrocardiographic characteristics, the probands were divided into 4 groups: Brugada (Br) pattern only, early repolarization (ER) pattern only, Br and ER patterns, and true IVF.

Results: The results of the genetic analysis revealed no S422L or other *KCNJ8* mutations and indicated no significant difference between the groups.

Conclusion: The *KCNJ8* mutation showed no association with JWS or IVF among our Japanese patients.

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1. Introduction

Ventricular fibrillation (VF) is the most malignant arrhythmia that causes sudden cardiac death. VF, which occurs in apparently healthy individuals without structural heart diseases, is regarded as an idiopathic or primary electrical disease. Among patients with idiopathic VF (IVF), an increased prevalence of early repolarization (ER) was observed, which was considered as a benign electrocardiographic (ECG) finding in the past [1]. Recently, the concept of J-wave syndrome (JWS), including the ER and Brugada (Br) syndromes, has emerged [2].

The mutation *KCNJ8*-S422L was first identified as the cause of ER syndrome in a 14-year-old Caucasian girl with VF. An ECG showed a prominent ER pattern in the inferolateral leads [3]. *KCNJ8* encodes an inward rectifier potassium 6.1 protein (Kir6.1),

which is a subunit of cardiac ATP-sensitive K (K_{ATP}) channels. The succeeding cases of the mutation were found in five men and two women with ER or Br syndrome [4,5]. However, whether *KCNJ8* mutations are present among the Asian population remains to be known. Therefore, the present study aimed to investigate the prevalence of *KCNJ8* gene mutation in Japanese patients with JWS or IVF.

2. Method

2.1. Study population

The study population was selected from unrelated families and consisted of 230 Japanese probands with IVF, Br syndrome, or suspected Br syndrome. All the probands underwent genetic analysis between 1996 and 2011 at the Shiga University of Medical Science and Kyoto University Graduate School of Medicine. Probands with structural heart diseases or other inheritable arrhythmic disorders were excluded from the study.

2.2. DNA isolation and mutation analysis

The genetic analysis protocol was approved by the institutional ethics committees of both universities and performed under the respective institutional guidelines. All the patients provided informed

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Abbreviations: Br, Brugada; ECG, electrocardiogram; ER, early repolarization; ICD, implantable cardioverter-defibrillator; IVF, idiopathic VF; JWS, J-wave syndrome

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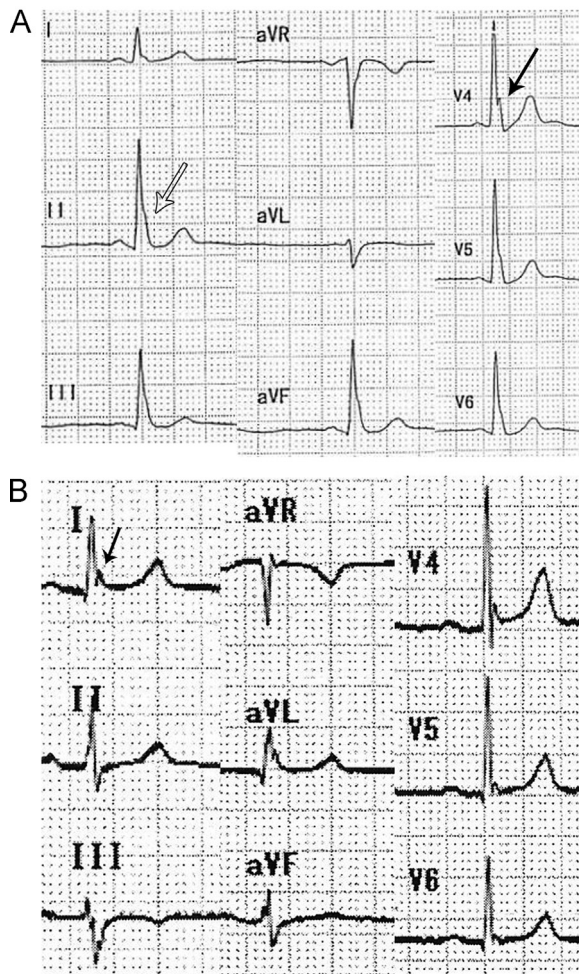


Fig. 1. Twelve-lead ECGs representing an early repolarization (ER) pattern. (A) ER pattern in the inferior and lateral leads. (B) ER pattern in the lateral leads only. Arrows indicate a slurring (opened) or notching (closed) ER morphology.

consent before undergoing the genetic analysis. Genomic DNA was isolated from leukocyte nuclei. We performed genetic screening for *KCNJ8*, *SCN5A*, *CACNA1C*, *CACNB2*, *SCN1B*, *KCNQ1*, *KCNH2*, *KCNE1-3*, and *KCNE5* using denatured high-performance liquid chromatography (WAVE System Model 3500, Transgenomic, Omaha, NE, USA) [6–8], high-resolution melting (LightCycler[®]480, Roche Diagnostics GmbH, Mannheim, Germany), and direct sequencing with the ABI PRISM 3130 sequencer (Applied Biosystems, Foster City, CA, USA). The cDNA sequence numbering of *KCNJ8* was based on the GenBank reference sequence (NC_000012). We excluded all the probands who had genetic test results positive for all the above-mentioned genes, except *KCNJ8*.

2.3. Clinical phenotype

We analyzed the following demographic characteristics in 230 patients: sex, age at diagnosis, history of symptoms, and indication for treatment with an implantable cardioverter-defibrillator (ICD). Patients who had a history of syncope or aborted cardiac arrest were considered symptomatic. The presence of Br [9] and ER patterns was examined using a 12-lead ECG. PR intervals, QRS durations, and QT intervals were manually measured in lead V₅. QTc intervals were calculated by correcting for heart rate using the Bazett formula. Patients in whom QTc values in resting ECG were lower than 350 ms^{1/2} or higher than 470 ms^{1/2} (men) and 480 ms^{1/2} (women) were also excluded [10].

2.4. Data analysis

The patients with JWS were stratified into 4 groups according to the following ECG characteristics: Br pattern only [9] (Br group), ER pattern only (ER group), overlapping Br and ER patterns (Br–ER group), or IVF with neither a Br nor ER pattern (true IVF group). Patients whose ECG displayed only a Br-type ST elevation in leads V₁ through V₃ [9] were categorized under the Br-only group, regardless of whether the Br pattern was spontaneous or drug induced. We defined ER as either a slurring or notching J-point elevation of at least 0.1 mV from the baseline in at least 2 conjugate leads (Fig. 1A and B) [11]. Patients who exhibited both Br and ER patterns were assigned in the Br–ER group, whereas those with VF/ventricular tachycardia whose ECG showed no Br or ER pattern were assigned in the true IVF group.

2.5. Statistical analysis

All continuous data were expressed as mean \pm standard deviation values. One-way analysis of variance with the Fisher least significant difference test and Games-Howell test was used for multiple comparisons. A $P < 0.05$ was considered statistically significant.

3. Results

3.1. Gene analysis

The gene analysis revealed that neither *KCNJ8*-S422L nor other *KCNJ8* mutations were present in our Japanese JWS and IVF cohorts. Nevertheless, we found a previously reported synonymous variant, p.I371 (c.C457T, rs112604741), in 2 probands, 1 who had VF belonged to the true IVF group and the other, who was asymptomatic, belonged to the Br–ER group. The mutation was absent in 112 healthy controls; however, the frequency of this SNP was reported to be 1.5% in heterozygotes (<http://www.ncbi.nlm.nih.gov/snp>).

3.2. Clinical characteristics

Table 1 presents the classification of the patients enrolled in this study according to clinical and ECG characteristics. The data of 230 probands (205, men) were included in the analysis. The patients' mean age at diagnosis was 45.1 ± 15.4 years. In terms of ECG characteristics, 135 patients had an ECG showing a Br pattern only; 15 an ER pattern only; and 53 Br and ER patterns. Only 27 patients with VF had no ECG abnormality.

The total clinical phenotypes are presented in Table 1. The symptomatic group included 72 patients who had experienced syncope and 75 who had an aborted cardiac arrest. Among the 230 probands, 88 (38%) had cardioverter-defibrillator implants. In the ECG analysis, the mean heart rate, PR, QRS, and QTc interval were 67.1 ± 13.6 bpm, 176.5 ± 25.8 ms, 94.6 ± 52.0 ms, and 404.2 ± 32.6 ms^{1/2}, respectively. Of the 230 patients, 188 (82%) had a Br ECG pattern (Br and Br–ER subgroups); 68 (30%), an ER pattern (ER and Br–ER subgroups); 53, (23%), Br and ER patterns; and 27 (12%), neither a Br nor ER pattern (true IVF).

Table 1 summarizes the clinical and ECG characteristics in the Br, ER, Br–ER, and true IVF groups. Male patients accounted for 89%, 87%, 96%, and 78% of the patients in the groups, respectively. The mean ages were similar in the 4 groups. Most of the ER and true IVF patients had experienced an aborted cardiac arrest compared with the Br and Br–ER patients (93% and 93% vs. 17% and 25%; $P < 0.0001$), indicating a statistically significant difference. The reason for the difference is that most of the patients in

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